“FORMULATION AND IN VITRO EVALUATION OF MEXILETINE HYDROCHLORIDE TIMED RELEASE CAPSULES

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INTRODUCTION

1.1 Oral drug delivery

Most convenient oral drug products such as tablets and capsule are formulated to release the active drug immediately after oral administration to obtain rapid and complete systemic drug absorption. Such immediate release products result in relatively rapid absorption and onset of accompanying pharmacodynamic effects. However, after absorption of the drug from the dosage form is complete, plasma drug concentrations decline according to the drugs pharmacokinetic profile. Eventually, plasma drug concentrations fall below the minimum effective plasma concentration (MEC), resulting in loss of therapeutic activity. Before this point is reached, another dose is usually given if a sustained therapeutic effect is desired. An alternative to administering another dose is to use a dosage form that will provide sustained drug release, and therefore maintain plasma drug concentrations, beyond what is typically seen using immediate- release dosage form. (Leon shargel *et al,* 2004).

The term modified – release drug product is used to describe products that alter the timing and/or the rate of release of the drug substance. A modified-release dosage form is define " as one for which the drug – release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms such as solution, ointments, or promptly dissolving dosage forms as presently recognized". Several types of modified-release drug products are recognized:

- Extended- release drug products: A dosage form that allows at least a twofold reduction in dosage frequency as compared to that drug presented as an immediate-release (conventional) dosage forms include controlled-release, sustained-release and long-acting drug products.

- Delayed-release drug products. A dosage form that releases a discrete portion of drug, at a time or at times other than promptly after administration, although one portion may be released promptly after administration. Enteric-coated dosage forms are the most common delayed-release products.

- Targeted-release drug products. A dosage forms that release drug at or near the intended physiologic site of action. Targeted-release dosage forms may have either immediate or extended-release characteristics.

1.2: Selection of Drug Candidate for Timed Release Dosage Forms

The physico – chemical properties of the drug such as pKa, partition coefficient, Biological half life, molecular weight, dose of the drug etc., have to be considered before selection. (Leon Lachman 1987).

Characteristics of drugs suitable for formulation as Timed Release Products

- Exhibit moderate rates of absorption and excretion.
- Uniform absorption throughout the gastrointestinal tract.
- Administered in relatively small doses.
- Possess good margin of safety.
- Used for treatment of chronic therapy.

Characteristics of drug unsuitable for formulation as Sustained Release Products

- Not effectively absorbed in the lower intestine *(*Riboflavin*)*
- Absorbed and excreted rapidly i.e. short biological half lives, less than one hour (Penicillin G, Furosemide).
- Long biological half lives greater than 12 hours (Diazepam, Phenytoin)
- Large doses required, (Sulphonamides)
- Drugs with low therapeutic index *(*Sulphonamides)
- No clear advantage for sustained release formulation (Griseofulvin)

1.3: Types of Oral Controlled Release Drug Delivery Systems

A number of techniques are used to achieve controlled release of drugs via the oral cavity. The majority of the oral controlled release systems relay on dissolution, diffusion or a combination of both mechanisms to generate slow release of drug.

- Dissolution controlled release systems
- Diffusion controlled release system
- Diffusion and dissolution system
- Osmotically controlled release system
- Gastroretentive drug delivery system
- Electrically stimulated release devices
- Ion-exchange resins

1.3.1: Dissolution Controlled Release Systems

A drug with a slow dissolution rate will sustain release rate of the drug from the dosage form. Here the rate-limiting step is dissolution. This being true, sustained release preparation of drug could be made by decreasing their rate of dissolution.

Dissolution controlled systems can be made either by

- Varying concentration of rate controlling coats or polymers (Matrix Dissolution Systems)
- By administering the drug as a group of beads that have coating of different thickness (Encapsulated Dissolution Systems)

Matrix Dissolution Systems are prepared by compressing the tablet with a slowly soluble polymer carrier into tablet form. Wax matrices are prepared either by congealing or dispersion the drug – wax mixture in water.

Encapsulated Dissolution Systems contain beads that have different coating thickness, their release will occur in a progressive manner. Those with the thinnest layer will provide the initial dose and the maintenance of drug levels at later times will be achieved from those with thicker coating. This dissolution process at steady state is described by the Noyes-Whitney equation. (Gilbert S. Banker et al, 2002).

$$dc/dt\ k_D(C_S\text{-}C) = DA/h\ (C_S\text{-}C)$$

Where

dc/dt = dissolution rate.

k_D = dissolution rate constant.

D = Diffusion coefficient.

C_S = Saturation solubility of solid.

C = Concentration of solute in the bulk solution

1.3.2: Diffusion Controlled Release Systems

In these systems the release rate of drug is determined by its diffusion through a water insoluble polymer. There are basically two types of diffusion devices. (Gilbert S. Banker et al, 2002).

1.3.2.1: Reservoir Devices:

Reservoir devices are characterized by a core of drug, the reservoir, surrounded by a polymeric membrane. The nature of the membrane determines the rate of release of drug. The methods used to develop reservoir type devices include micro-encapsulation of drug particles and coating of tablet containing drug cores.

Advantage:

i) These devices can offer zero-order release of the drug.

ii) Avoid patient compliance problem.

iii) Employ less total drug.

Disadvantage:

i) System must be physically removed from implant sites.

ii) Difficult to deliver high molecular weight compounds.

1.3.2.2: Matrix Device

The three major types of materials used in the preparation of matrix devices are insoluble plastics, hydrophilic polymers and fatty compounds. The most common method of preparation is to mix the drug with the matrix material and then

compress the mixture. The drug release from a porous or granular matrix can be described by

$$M= (D_s.C_a.\{P/T\}.[2C_0-PC_a]t)^{1/2}$$

Where

P = Porosity of the matrix

T = Tortuosity

C_a = Solubility of the drug in the release medium

D_S = Diffusion coefficient in the release medium

1.3.3.Diffusion and Dissolution Controlled Systems

In these systems the release rate of drug is determined by both the diffusion and dissolution mechanisms. The drug core is encased in partially soluble membrane. Pores are thus created due to dissolution of parts e membrane which permit entry of aqueous medium into the core and hence drug dissolution and allow diffusion of dissolved drug out of the system. (Gilbert S. Bakers et al, 2002).

1.3.4. Osmotically Controlled Release Systems

The osmotic pump represents a newer concept in extended-release preparations. Drug delivery is controlled by the use of an osmotically controlled device that promotes a constant amount of water into the system, either by dissolving and releasing a constant amount of drug per unit time or by the use of a "push-pull" system that pushes the drug out at a constant rate as water flows into an expandable osmotic compartment. Drug is release via a single laser-drilled hole in the tablet.

A representative osmotic oral drug product is the "push-pull" system called Gastro intestinal Therapeutic System (GITS), developed by Alza Corporation for nifedipine (Procardia XL) and other drugs. The system consists of a semi permeable membrane and a two-layer core of osmotic ingredient and active drug. As water enters the system, the osmotic pressure builds up from the inner layer, pushing the drug out through a laser-drilled orifice in the drug layer. (Leon Shargel et al, 2004).

1.3.5: Gastro retentive Drug Delivery Systems

Dosage forms that can be retained in stomach are called Gastro retentive Drug Delivery System (GEDDS). GRDDS can improve the controlled delivery of drugs that have an absorption window by continuously releasing the drug for a prolonged period of time before it reaches its absorption site thus ensuring its optimal bioavailability.

The approaches that have been pursued to increase the retention of an oral dosage form in the stomach include Bioadhesive systems, swelling and expanding systems, High density systems and Low density (Floating) systems.

1.3.5.1: Bioadhesive Systems

Bioadhesion is the process whereby synthetic and natural macromolecules adhere to the biological membranes in the body and remain there for an extended period of time. If the membrane substrate is mucosal layer then the process is referred to as mucoadhesion. The bioadhesives increase the residence time and contact time at the area of absorption and provide a high concentration gradient across the membrane.

1.3.5.2: Swelling and Expanding Systems

These system increases the residence time of the dosage form in the stomach. Particles greater than 10mm are unable to enter the duodenum and are retained in the stomach. The swelling systems incorporate hydrogels which are polymers that can swell up to 100 times their dry weight. The hydrogels used must be biodegradable.

1.3.5.3: High Density Systems

In high density system the bulk density of the dosage form must exceed that of normal stomach and should be at least 1.40. In preparing such formulations, drug can be coated on a core with heavy, inert material such as barium sulfate and titanium dioxide. The weighed pellet can then be covered with a diffusion controlled membrane.

1.3.5.4: Low Density (Floating) Systems

Floating drug delivery system (FDDS) have a bulk density less then gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system in floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system in emptied from the stomach. This results in an increased GRT and a better control of fluctuations in plasma drug concentration. These systems are suitable for drugs that are poorly soluble or unstable in the intestinal medium.

1.3.6: Electrically Stimulated Release Devices

These are monolithic devices prepared by using polyelectrolyte gels which swell when an external electrical stimulus is applied, causing a change in PH. The release could be modulated, by the current, giving a pulsatile release profile. Precise control over the release of drug from devices implanted in the body, such as quantity, timing, is highly desirable in order to optimize drug therapy. Electrically-controllable drug release from polyelectrolyte hydrogels is helpful in achieving these goals.

The mechanism of drug release include ejection of the drug from the gel as the fluid phase synereses out, drug diffusion along a concentration gradient, electrophoresis of charged drugs towards and oppositely charged electrode and liberation of the entrapped drug as the gel complex erodes.

1.3.7: Ion-Exchange Resins

Ion exchange systems use resins composed of water insoluble cross linked polymers. These polymers contain salt-forming functional groups in repeating positions on the polymer chain. The drug is bound to the resin and released by exchanging with appropriately charged ions in contact with the ion-exchange groups.

$$Resin^{+} - Drug^{-} + X^{-} \longrightarrow Resin^{+} - X^{-} + Drug^{-}$$

$$Resin^{-} - Drug^{+} + Y^{+} \longrightarrow Resin^{-} - Y^{+} + Drug^{+}$$

Where X^{--} and Y^{+} are ions in the GI tract. The free drug then diffuses out of the resin. The drug-resin complex is prepared either by repeated exposure of the resin to the drug in a chromatography column or by prolonged contact in solution.

The rate of drug diffusing out of the resin in controlled by the area of diffusion, diffusional path length and rigidity of the resin, which is a function of the amount of cross-linking agent used to prepare the resin. An improvement in this system is to coat the Ion-exchange resin with a hydrophobic rate-limiting polymer, such as ethyl cellulose or wax. These systems rely on the polymer coat to govern the rate of drug availability. (Gilbert S.Banker et al) 2002.

1.4. Factors influencing the design and performance of Timed release products

The design of controlled - release delivery system is subjected to several variables of considerable importance. Among these, the properties of the drug, the route of drug delivery, and the disease being treated and length of the therapy have major importance.

1.4.1. Physicochemical factors

- Aqueous solubility
- Partition coefficient
- Drug stability
- Protein binding
- Molecular size and Difrusivity

1.4.2. Biological factors

- Absorption
- Distribution
- Elimination
- Biological half life and Duration of action
- Side effects and Margin of safety
- Dose size
- Disease state

1.4.3. Physicochemical factors

- **Aqueous solubility:**

The aqueous solubility of a drug influences its dissolution rate, which in turn establishes its concentration in solution and hence the driving force for diffusion across membrane. The choice of mechanism for oral Timed release systems is limited by aqueous solubility of the drug. Diffusional systems will be poor choices for slightly soluble drugs since the driving force for diffusion; the concentration in aqueous solution will be low. Such drugs may be effectively incorporated in matrix system.

- **Partition coefficient:**

Partition coefficient ($K_0/_W$) is defined as the ratio of the fraction of the drug in an oil phase to that of an adjacent aqueous phase.

$K=Co/C_w$

Where

Co = Equilibrium concentration of all forms of the drug e.g. ionized and unionized in an organic phase at equilibrium

C_w= Equilibrium concentration of all forms in aqueous phase

Accordingly, compounds with a relatively high $K_{0/w}$ are predominantly lipicl-soluble and consequently, have very low aqueous solubility. Furthermore, these compounds can usually persist in the body for long periods as they can localize in the lipid membranes of cells, (e.g.: Phenothiazines). Compounds with very low $K_0/_w$will have difficulty in penetrating membranes, resulting in poor bioavailability. Furthermore, partitioning effects apply equally to diffusion through polymer membranes. The choice of diffusion-limiting membranes must largely depend on partitioning characteristics of the drug. Drugs with a partition coefficient that is higher or lower than the optimum (i.e., 1000/1) in general, are poor candidates for formulation into Timed dosage forms,

- **Drug stability**

Orally administered drugs can be subject to both acid base hydrolysis and enzymatic degradation. For drugs like Propantheline that are unstable in the stomach, the most appropriate controlling unit would be the one that releases its contents only in the intestine. The reverse in the case for drugs like Probanthine that are unstable in the environment of the intestine, the most appropriate controlling unit in this case would be one that releases its contents only in the stomach. In general, drugs with significant stability problems in any particular area of the gastrointestinal tract are less suitable for formulation into Timed release systems.

- **Protein binding:**

Many drugs bind to plasma proteins with a significant influence on the duration of drug action. If a drug has binding properties with a particular protein, then the distribution of the drug into the extra vascular space is governed by the equilibrium process of dissociation of the drug from the protein. The drug-protein complex can serve therefore as a reservoir in the vascular space for controlled drug release to extra vascular tissues, but only for those drugs that exhibit a high degree of binding. Extensive binding to plasma proteins will be evidenced by a long half-life of elimination for the drug and such drugs generally do not require a Timed release dosage form.

- **Molecular size and Diffusivity:**

Drugs in most of the Timed release systems must diffuse through a rate controlling membrane or matrix. The ability of a drug to diffuse through these membranes is known as diffusivity (diffusion coefficient). This diffusivity is a function of its molecular size (or molecular weight) and is related by the equation.

$$\mathbf{Log\ D = S_v log_v + K_v = S_m log M + K_m}$$

Where

D = diffusivity

M = molecular weight

V = molecular volume

S_v, S_m, K_v and K_m = constants in a particular system.

In general the denser the medium, the smaller is the diffusivity.

1.4.4. Biological factors

The design of sustained release products should be based on a comprehensive picture of drug disposition. This would entail a complete examination of the ADME characteristics of a drug following multiple dosing.

Absorption:

The rate, extent and uniformity of absoiption of a drug are important factors when considering it's formulation into a sustained release dosage form. To maintain a constant blood or tissue level of drug, it must be uniformly released from the sustained release system and then uniformly absorbed. Since the rate-limiting step in drug delivery from a sustained release product is its release from a dosage form, a rapid rate of absorption of drug relative to its release is essential if the system is to be successful. In case of sustained release dosage form, the rate constant for drug release is much less than the constant for drug absorption (i.e., $K_r << K_a$). Assuming that the transit time of a drug through the absorption area of the gastro intestinal tract is between 9 and 12 hrs, the maximum absorption half-life should be 3 to 4 hrs. This corresponds to a minimum absorption rate constant $K._a$ of 0.17 to 0.23 hr" necessary for about 80 to 95 % absorption over a 9 to 12 hr transit time. For a drug with a very rapid rate of absorption (i.e., $K,_a$» 0.23 $hr"^{1}$), the above discussion implies that a first order release rate constant K_r < 0.17 hr'^{1} is likely to result in unacceptably poor bioavailability in many patients. Therefore, slowly absorbed drugs will be difficult to formulate into Timed release dosage forms.

Distribution:

Two parameters that are used to describe the distribution characteristics of a drug are its apparent volume of distribution (V,j) and the ratio of drug concentration in the tissue to that in plasma (T/P ratio) at the steady state. In general, the bound portion of drug can be considered inactive and unable to cross membranes. At high binding one sees prolonged drug action. The apparent volume of distribution of a drug is frequently used to describe the magnitude of distribution, including binding, within the body. The total apparent volume of distribution for a drug at steady state can be calculated from the following equation.

$$V_{dss}=[(k_{l2}+k_{21})/k_{2l}]V_p$$

Where,

Vd_{ss} is the apparent volume of distribution at steady state and FC_2i are the constants for the distribution of drug from the central to peripheral compartment and from peripheral to central compartments respectively.

V_p is the volume of central compartment.

Elimination:

Elimination of a drug involves two aspects i.e., metabolism and excretion. Metabolism of a drug can either inactivate an active drug or convert an inactive drug to an active metabolite. Drugs that are significantly metabolized before absorption, either in the lumen or tissue of the intestine, can show decreased bioavailability particularly from slowly releasing dosage forms. Metabolism of a drug will be reflected in the elimination rate constant of a drug or by the appearance of a

metabolite. It is possible to incorporate this pharmacokinetic property into the design of sustained release product, provided that the rate and extent of metabolism are predictable and that the rate constant(s) for the process are not too large. Undoubtedly, complex metabolic patterns would make the design much more difficult, particularly when biological activity is wholly or partly due to a metabolite, as is the case of Isosorbide 2,5-dinitrate.

Biological half life and Duration of action:

The usual goal of an oral Timed release product is to maintain therapeutic blood levels over an extended period. The elimination rate is quantitatively described by the half-life. The biological half-life and hence duration of action of a drug obviously play a major role in the process of considering a drug for sustained release. Therapeutic compounds with a short half-life are excellent candidates for sustained-release preparations, since this can reduce dosage frequency. However, this is limited, in that drugs with very short biological half life as it may require excessively large amounts of drug in each dosage unit to maintain sustained effect.

In general, drugs with half-life shorter than two hours are poor candidates for sustained release preparations. Drugs with long half-life, more than 8 hrs, are also generally not used in sustaining forms, since their effect is already sustained.

Side effects and Margin of safety:

Theoretically, the incidence of side effects can be minimized by controlling the concentration at which the drug exists in plasma at any given time, and hence controlled release formulations appear to offer a solution to this problem. By slowing the rate at which the drugs are released, the chances of gastrointestinal

irritation will be reduced due to a smaller amount of drug exposed to the gastrointestinal mucosa at the given time. The most widely used measure of the margin of safety of a drug is its therapeutic index (TI).

= TD50/ED50

Where,

= median toxic dose = median effective dose

Drugs with very small value of therapeutic index usually are poor candidates as sustained release products.

Dose Size:

For orally administered systems, there is an upper limit to the bulk size of the dose to be administered. In general a single dose of 0.5 to Igm is considered maximum for conventional dosage form. This also holds for Timed release dosage forms.

Disease State:

Sometimes the disease states are considered before the designing of an oral SR dosage form. This can be explained by taking the example of Aspirin (for rheumatic arthritis) which is not a suitable candidate for Timed release dosage form. Still an aspirin sustained release dosage form could be advantageous to maintain therapeutic concentrations, particularly throughout the night, thus alleviating morning stiffness.

1.5. TIMED-RELEASED DRUG DELIVERY:

Timed-release dosage forms are designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose. The basic intention of any drug delivery system is to provide a therapeutic amount of drug to proper site in the body of promptly achieve and then maintain the desired drug concentration. Extended release dosage form that shows at least a twofold reduction dosage form and various example of extended release dosage forms included controlled-release, sustained-release, and long acting drug product and different types of extended release products include drug release from matrix, gum-type matrix tablets, polymeric matrix tablet, ion-exchange, core tablets, microencapsulation, osmotic extended release etc.(shargel, 2005).

Oral administration has been known from decades as the most widely used route of drug administration amongst all routes that have been explored for the systemic delivery of drugs via various pharmaceutical products of different dosage forms (chein 1992). In the recent years, scientific and technological advancement have been made in research and development of rate controlled oral drug delivery system by overcoming various physiological constraints, such as short residence time and unpredictable gastric emptying time (Forman *et al,* 1994*)*. Pulsatile drug delivery and timed-release drug delivery are among such advances. There are many drugs that are more effective when given to the patient in a pulsatile manner as opposed to a continuous release fashion.

Traditionally, drug delivery has meant in getting a simple chemical absorbed predictably from the gut or from the site of injection. A second-generation drug delivery goal has been the perfection of continuous, constant rate delivery of bioactive agents. However, living organisms are not ‘’’zero-order”” in their requirement or response to drugs. They are predictable resonating dynamic systems, which require different amounts of drug at predictably different times within the circadian cycle which will maximize desired therapeutic effects and minimize undesired drug effects. (survase S, kumar N2007)

In case of chronic treatment, where the drug is given in sustained release dosage form, continuous exposure of the drug to body may lead to adverse effect. (drugbank 2005).

1.5.1. Advantages of timed-release drug delivery:

- Prolonged administration of therapeutic dose at the desired delivery rate.
- Avoid patient compliance problem.
- Employ less total drug.
- Obtain less potentiating/reduction in drug activity with chronic use.
- Minimize drug accumulation with chronic dosing.
- Improve efficiency of treatment.
- Improve control of condition, i.e., reduce fluctuation in drug level.
- Increased safety margin of high potency drugs due to control of plasma levels.(Brahmankar DM and Jaiswal SB 2000).

1.5.2 Disadvantages of timed-release drug delivery:

- Decreased systemic availability in comparison to immediate release conventional dosage forms; this may due to incomplete release, increased first pass metabolism, increased instability, insufficient residence time for complete release, site-specific absorption, pH dependent solubility.
- Poor *in-vitro-in-vivo correlation*.
- Possibility of dose dumping due to food interaction.
- Retrieval of drug is difficult in case of toxicity, poisoning or hypersensitivity reactions.
- Reduced potential for dosage adjustment of drugs normally administered in varying strengths.
- Higher cost of formulation.

Mexiletine hydrochloride is an anti-arrhythmic agent, used for ventricular arrhythmia. A marketed product of this drug is given in capsule form thrice a day.

Hence, a timed-release dosage form of mexiletine hydrochloride has been investigated to deliver the doses at different time intervals in a pulsatile manner. Instead of taking three doses at three different time intervals per day, the patient will have to take one timed release capsule leading to better patient compliance.

1.6. Introduction to the arrhythmias:

The arrhythmias are conceptually simple dysfunctions cause abnormalities in impulse formation and conduction in the myocardium. However, in the clinic,

arrhythmias present as a complex family of disorders that a show a variety of symptoms. For example, cardiac arrhythmias may cause the heart,(mary*et.al,*2000*)*

1. To beat too slowly (sinus bradycardia.)

2. To beat too rapidly (sinus or ventricular tachycardia, atria or ventricular premature depolarization).

3. To respond to impulses originating from sites other than a SA node.

4. To respond to impulses travelling along accessory pathways that lead to deviant depolarization.

In order to make sense of this large group of disorders, it is useful to organize the arrhythmias into groups according to the anatomic site of the abnormality-the atria, AV node, or the ventricles.

Causes of Arrhythmias

Most arrhythmias arise either from aberrations in impulse generation or from a defect in impulse conduction.

Abnormal automaticity

The SA node shows the fastest rate of Phase 4 depolarization and therefore, exhibits a higher rate of discharge than that occurring in other pacemaker cells exhibiting automaticity. The SA node thus normally sets the pace of contraction for the myocardium, and latest pacemakers are depolarized by impulses coming from the SA node. However, if cardiac sites other than the SA node show enhanced automaticity, they may generate competing stimuli, and arrhythmias may arise.

Abnormal automaticity may also occur if the myocardial cells are damaged, for example, by hypoxia or potassium imbalance. These cells may remain partially depolarized during diastole and therefore can reach the firing threshold earlier than normal cells. Abnormal automatic discharges may thus induce arrhythmias.

Effect of drugs on automaticity

Most of the anti-arrhythmic agents suppress automaticity by decreasing the slope of Phase 4 depolarization and or by raising the threshold of discharge to a less negative voltage. Such drugs cause the frequency of discharge to decrease, an effect that is more pronounced in cells with ectopic pacemaker activity than in normal cells.

Abnormalities in impulse conduction

Impulses from higher pacemaker centers are normally conducted down pathways that bifurcate to activate the entire ventricular surface. A phenomenon called re-entry can occur if a unidirectional block caused by myocardial injury or prolonged refractory period results in an abnormal conduction pathway. Re-entry is the most common cause of arrhythmias and can occur at any level of the cardiac conduction system. For example consider a single purkinje fiber with two conduction pathways to ventricular muscle. An impulse normally travels down limbs of the conduction path. However, if myocardial injury results in a unidirectional block, the impulse may only be conducted down pathway. If the block in pathway is in the forward direction only, the impulse may travel in a retrograde fashion through pathway and re-enter the point of bifurcation. This short-

circuits pathway results in reexcitation of the ventricular muscle, causing premature contraction or sustained ventricular arrhythmia.

Effects of drugs conduction abnormalities:

Anti-arrhythmic agents prevent re-entry by slowing conduction and or increasing the refractory period required to convert a unidirectional block into a bidirectional block.

Classifications of 0 phase anti-arrhythmic agents:

1) Membrane stabilizing agents (Na^+ channel blockers)

Moderately decrease dv/dt of 0 phase –

Quinidine, Procainamide.

Little decrease in dv/dt of 0 phase –

Lidocaine, Mexiletine HC1.

Marked decrease in dv/dt of 0 phase –

Propafenone, Flecainide.

2) Antiadrenergic agents (beta blockers) –

Propranolol, Esmolol.

3) Agents widening AP –

Amiodarone, Bretylium, Dofetilide

4) Calcium channel blockers –

Verampil, Dilitazem

Mexiletine hydrochloride comes under the class of membrane stabilizing agents and used as an anti-arrhythmic agent for decreasing ventricular arrhythmia's and belongs to chemical class of di methyl benzene derivatives.(Tripati KD 2006).

1.7. Classification of Pulsatile drug delivery system:

Pulsatile drug delivery system can be classified as site-specific and time-controlled systems. Drug release from site-specific systems depends on the environment in the gastro intestinal tract, e.g., on pH, presence of enzymes, and the pressure in the gastrointestinal tract. In contrast, time-controlled DDS are independent of the biological environment. The drug release is controlled only by the system. Time-controlled pulsatile delivery has been achieved mainly with drug-containing cores, which are covered with release-controlling layers. (Gathoskar*et.al,* 2004, Shivakumar *et.al,*2003)

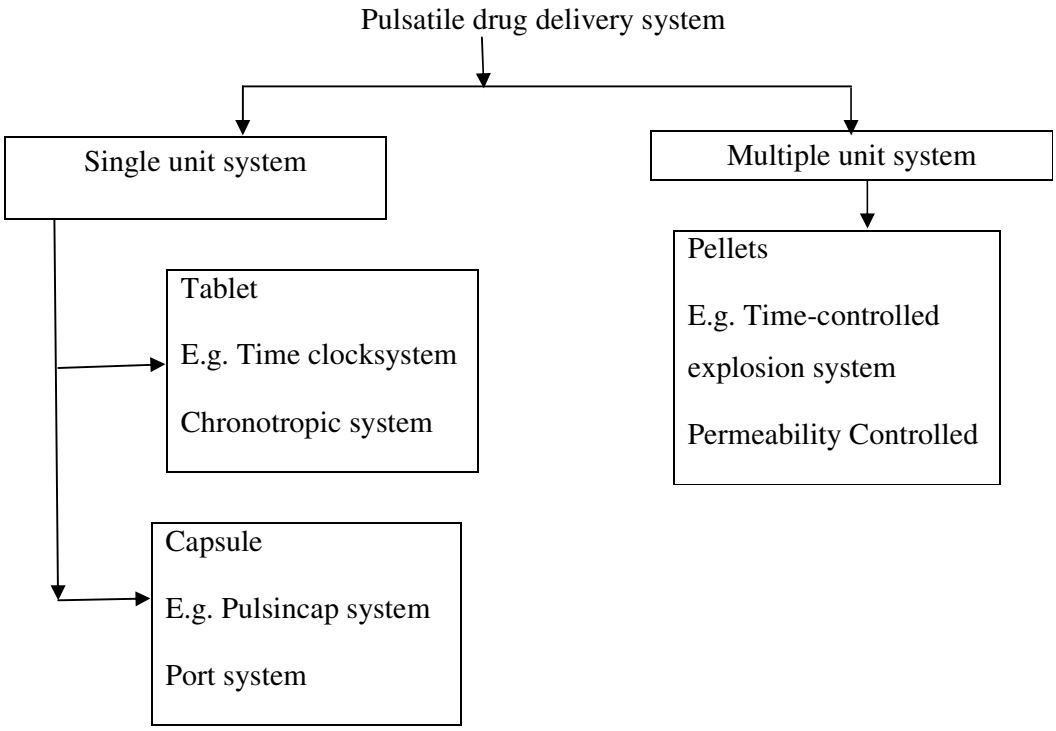


Fig 1. Classification of pulsatile drug delivery

Traditionally, drug delivery has meant getting a simple chemical absorbed predictably from the gut or from the site of injection. A second-generation drug delivery has been the perfection of continuous, constant rate delivery of bioactive agents. However, living organisms are not "zero-order" in their requirement or response to drugs. They are predictable resonating dynamic systems, which require different amounts of drug at predictably different times within the circadian cycle which will maximize desired and minimize undesired drug effects.(Youan B 2004)Till early 1990s efforts have been made to design the drug delivery system which will release the drug at fairly constant rate.

In fact these systems turned to be one of the most successful systems in delivering the drug molecule.(Maroni *et.al,*2005) but still for many of the drugs, use of such systems is not suitable because of a number of reasons. This is particularly true in cases where the drug is subjected to large metabolic degradation. Due to 'first pass effect' there will be reduction in the bioavailability of the drug because gradual release can result in greater degradation. Secondly drugs with short half-life need to be administered repeatedly which results in patient non-compliance. Further, in case of chronic treatment, where the drug is given in sustained release dosage form, continuous exposure of the drug to body may lead to adverse effect. Lastly, drugs which exhibit tolerance should not be delivered at a constant rate, since the drug effect decreases with time at constant drug level. In addition drug toxicity increases with time when drug levels are held constant. In such cases it is preferable to choose a dosage form which will provide desired concentration of drug at particular time point only. (Pozzi *et.al,*2005)

Now a days, concept of chronopharmaceutics has emerged, wherein, research is devoted to the design and evaluation of drug delivery systems that release a therapeutic agent at a rhythm that ideally matches the biological requirement of a given disease therapy. Diseases where a constant drug levels are not preferred, but needs a pulse of therapeutic concentration in a periodic manner acts as a push for the development of "Pulsatile Drug Delivery Systems". (Siegel RA and Pitt CG 1995).

In these systems, there is rapid and transient release of a certain amount of drug molecules within a short time-period immediately after a predetermined off release period. Various techniques are available for the pulsatile delivery like pH dependent systems, time dependent systems, micro-flora activated systems, etc. which can be designed as per the physiology of disease and properties of the drug molecule. The focus of the present review is primarily on the pulsatile drug delivery methodologies and the upcoming technologies, which are being exploited on an industrial scale.

1.7.1 Methodologies for Pulsatile drug delivery

Methodologies for the pulsatile drug delivery system can be broadly classified into three classes,

1. Time controlled

2. Stimuli induced

3. Externally regulated

In time controlled drug delivery systems pulsatile release is obtained after a specific time interval in order to mimic the circadian rhythm. Such type of pulsatile

drug delivery system contains two components: one is immediate release type and other one is a pulsed release type.

In these systems there is release of the drug after stimulation by any biological factor like temperature, or any other chemical stimuli. These systems are further classified into temperature induced systems and chemical stimuli induced system, on the basis of stimulus.

In these systems there is a release of the drug after externally controlled device like an automatic motor or remote oriented control. By an externally fixed device we can control the release of a device and its action.

2. REVIEW OF LITERATURE

Hyun Seok Hwang *et al*, (2011) had found that Inhibition of cardiac calcium release channels determines efficacy of class I Antiaarrhythmic drugs in catecholaminergic polymorphic ventricular tachycardia. Catecholaminergic polymorphic ventricular tachycardia (CPVT) is caused by mutations in the cardiac ryanodine receptor (RyR2) or calsequestrin (Casq2) and can be difficult to treat. The class Ic antiarrhythmic drug flecainide blocks RyR2 channels and prevents CPVT in mice and human. They first measured the effect of all class I antiarrhythmic drugs marketed in the United States (quinidine, procainamide, disopyramide, lidocaine, mexiletine, flecainide, and propafenone) on single RyR2 channels incorporated into lipid bilayers. Only flecainide and propafenone inhibited RyR2 channels, with the S-enantiomer of propafenone having a significantly lower potency than R-propafenone or flecainide. In $Casq2^{-/-}$ myocytes, the propafenone enantiomers and flecainide significantly reduced arrhythmogenic Ca^{2+} waves at clinically relevant concentrations, whereas Na^{+} channel inhibitors without RyR2 blocking properties did not.RyR2 cardiac Ca^{2+} release channel inhibition appears to determine efficacy of class I drugs for the prevention of CPVT in $Casq2^{-/-}$ mice. Propafenone may be an alternative to flecainide for CPVT patients symptomatic on β-blockers.

Xiaoxiong Wei *et al.,* (1999) The objectives of this study were to characterize the inhibitory effects of mexiletine, lidocaine, and tocainide on cytochrome P-450 1A2 (CYP1A2) activity in human liver microsomes and to evaluate their relative inhibitory potencies by using a molecular model of this P-450 isozyme. The inhibitory effect of mexiletine, lidocaine, and tocainide on cytochrome CYP1A2 in human liver microsomes was examined with methoxy resorufin*O*-demethylase

activity as an index of the catalytic activity of this P-450 isozyme. The kinetic inhibition types and K_i values were determined by Lineweaver-Burk plots and Dixon plots, respectively. Molecular modeling was used to assess the interaction of these agents with the CYP1A2 active site. Methoxyresorufin *O*-demethylase activity was inhibited 67 ± 8%, 20 ± 5%, and 7 ± 4% by 2 mm *mexiletine, lidocaine, and tocainide*, respectively. *Mexiletine and lidocaine* exhibited competitive inhibition with K_i values of 0.28 ± 0.12 mM and 1.54 ± 0.74 mM, respectively, whereas the inhibition type of tocainide could not be determined because of its weak potency. A charge interaction between mexiletine and the Asp313 side chain in the CYP1A2 active site was found, and varying degrees of hydrogen bond formation between these three compounds and the CYP1A2 active site were observed. The *in vitro* inhibitory potencies in human liver microsomes (mexiletine>lidocaine>tocainide) are consistent with the structural interactions found in a molecular model of the active site of CYP1A2.

YuanfengGao, *et al.* (2013), studied that Inhibition of Late Sodium Current by Mexiletine: A Novel Pharmotherapeutical Approach in Timothy Syndrome is a rare LQTS caused by *CACNA1C*mutations G406R in exon 8A (TS1) and G402S/G406R in exon 8 (TS2). mexiletine, to improve clinical manifestations in TS.Therapeutic effects of mexiletine were evaluated using ECG and Holter monitoring. The electrophysiologic effect of mexiletine was evaluated in a TS model using rabbit ventricular wedges. The proband with severe syndactyly and delayed language skills was identified harboring a G406R mutation in *CACNA1C*. Though asymptomatic he exhibited mild QTc prolongation (470-490 ms) and syndactyly. Mexiletine shortened QTc from 584 to 515 ms, blunted QT-RR relationship, and abolished 2:1

AVB and TWA in the girl. In *in-vitro* studies, *mexiletine* inhibited late I_{Na} with IC_{50} of 17.6±1.9 μM and attenuated brady-dependent QT prolongation and reduced QT-RR slope in the TS model using BayK 8644. *Mexiletine* shortened QTc, attenuated QT-RR slope, abolished 2:1 AV block and TWA in a TS1 patient and TS model via inhibition of late I_{Na}.

Asano K *et al.,* (2003) found out that Attenuating effect of mexiletine hydrochloride on herpetic pain in mice infected with herpes simplex virus.The influence of mexiletine hydrochloride on herpes-related pain responses was examined using mice infected with herpes virus. BALB/c mice were inoculated with herpes simplex virus (HSV; 1×10^6 plaque-forming units) on the right hind paw, and the contralateral hind paw was without inoculation. The changes in nociceptive threshold were examined using electric von fray meter. BALB/c mice inoculated with HSV showed a decrease in nociceptive threshold. Intraperitoneal administration of *mexiletine* prevented the decrease in nociceptive threshold dose-dependently in HSV-inoculated mice, which was firstly observed at a dose of 15.0mg kg^{-1}, and peaked at doses more than 17.5 $mgkg^{-1}$. This antinociceptive effect of mexiletine attained peaks at 60-90 min after administration and declined gradually to non-treated levels by 150min. mexiletine scarcely affected noradrenaline (norepinephrine) levels in the pons and medulla oblongata,even when HSV-inoculated mice were treated with 17.5mg kg^{-1} mexiletine. These results strongly suggested that mexiletine exerts antinociceptive effects on herpes-related pain through enhancement of β-endorphin levels in the central nervous system in HSV-inoculated mice. It is also suggested that mexiletine will be a good candidate for an antinociceptive drug in the treatment of acute herpetic pain in man.

Ging Kuo Wang *et al.,* (2004), studied *Mexiletine* block of wild-type and inactivation-deficient human skeletal muscle hNav1.4 Na^+ channels. *Mexiletine* is a class 1b antiarrhythmic drug used for ventricular arrhythmias but is also found to be effective for paramyotoniacongenita, potassium-aggravated myotonia, long QT–3 syndrome, and neuropathic pain. This drug elicits tonic block of Na^+ channels when cells are stimulated infrequently and produces additional use-dependent block during repetitive pulses. We examined the state-dependent block by *mexiletine* in human skeletal muscle hNav1.4 wild-type and inactivation-deficient mutant Na^+ channels (hNav1.4-L443C/A444W) expressed in HEK293t cells with a β1 subunit. The 50% inhibitory concentrations (IC_{50}) for the inactivated-state block and the resting-state block of wild-type Na^+channels by mexiletine were measured as 67.8 ± 7.0 μM and 431.2 ± 9.4 μM, respectively (*n*= 5).

Zeynep aydogmus *et al.,* (2002) developed a new spectrophotometric method based on the formation of an ion-pair using bromothymol blue as ion-pair complexing reagent for the determination of mexiletine hydrochloride in capsules. The ion-pair formed was highly coloured and easily extracted with dichloromethane. The calibration curve was linear over the concentration range 1.08{10.8 g.ml −1 at _*max* = 408 nm (r = 0.9999). The results obtained from the developed method were compared statistically with those obtained by the British Pharmacopeia method.

Fukui *et al*., (2004) Prepared enteric coated timed-release press-coated tablets and evaluation of their function by *in vitro and in vivo* tests for colon targeting As a new oral drug delivery system for colon targeting, enteric coated timed-release press-coated tablets (ETP tablets) were developed by coating enteric polymer on timed-release press-coated tablets composed of an outer shell of hydroxypropylcellulose

and core tablet containing diltiazem hydrochloride (DIL) as a model drug. The results of the in vitro dissolution tests in JP 1st fluid (pH 1.2) and JP 2nd fluid (pH 6.8) indicated that these tablets showed both acid resistance and timed-release. To clarify whether ETP tablets could have been of use in the gastrointestinal tract, ETP tablets with a layer of phenylpropanolamine hydrochloride (PPA) (a marker of gastric emptying) between the enteric coating layer and outer shell were prepared, and were administered to beagle dogs. Also, the results seemed to be in accordance with the time at which the tablets reached the colon after gastric emptying. Therefore, ETP tablets seemed to be an effective tool for oral site-specific delivery including targeting of the colon.

Saita *et al,* (2003) Development of enzyme-linked immunosorbent assay for therapeutic drug monitoring of mexiletine. Anti-mexiletine antibody was obtained by immunizing rabbits with an antigen conjugated with mercaptosuccinyl bovine serum albumin using N-(epsilon-maleimidocaproyloxy) succinimide as a heterobifunctional coupling agent. Enzyme labeling of mexiletine with beta-D-galactosidase was performed using glutaraldehyde. In this assay, the mexiletine to be quantified is chemically modified by acetic anhydride allowed to compete with a mexiletine-beta-D-galactosidase conjugate for binding to a limited amount of an anti-mexiletine antibody which was used to coat the wells of a microtiter plate. This assay was specific for mexiletine and showed very slight cross-reactivity with its major metabolite, 2-hydroxymethylmexiletine (1.5%), but none with p-hydroxymexiletine. The values of serum mexiletine levels from 15 patients by this enzyme-linked immunosorbent assay were comparable with those measured by HPLC. There was a good correlation between the values determined by the two

methods. The enzyme-linked immunosorbent assay should be a valuable tool in therapeutic drug monitoring and pharmacokinetic studies of mexiletine.

Sawada *et al.,* (2003) created a new index, the core erosion ratio, of timed-release tablets acetaminophen and its bioavailability. Although compression-coated tablets are a commonly used timed-release drug delivery technology, their utility is often limited by poor bioavailability. To try to improve the bioavailability of these tablets, the effect of their core composition of compression-coated tablet on in vivo pharmacokinetics was investigated. First, the extent of mass reduction of cores in different compression-coated tablet core formulations was used to establish a new index, the core erosion ratio. The data show that adding excipients with high water solubility to the core results in a greater core erosion ratio. Next, to elucidate the effect of core erosion ratio on in vivo acetaminophen (AAP) release, three compression-coated tablet formulations with similar in vitro AAP release profiles but different core erosion ratios were administered to four fasted dogs. These results suggest that a formulation with a large core erosion ratio can significantly increase in vivo drug release from compression-coated tablets, leading to increased drug absorption from the lower GI tract.

Andrei et al., (2006) The objective of this study was to develop and evaluate a pulsatile multiparticulate drug delivery system (DDS), coated with aqueous dispersion Aquacoat® ECD. A rupturable pulsatile drug delivery system consists of (i) a drug core; (ii) a swelling layer, comprising a superdisintegrant and a binder; and (iii) an insoluble, water-permeable polymeric coating. Upon water ingress, the swellable layer expands, resulting in the rupturing of outer membrane with subsequent rapid drug release.In contrast, a sustained release was achieved after the

lag time, when low-substituted hydroxypropyl cellulose (L-HPC) and sodium starch glycolate (Explotab®) were used as swelling agents. The optimal level of AcDiSol® to achieve a fast and complete release after the lag time was 26% (w/w) (based on the weight of the coated pellets).

Sawada *et al.,* **(2004)** Time-release compression-coated core tablet containing nifedipine has been formulated and evaluated for chronopharmacotherapy. Compression-coated time-release tablets (CC tablets) containing nifedipine, dihydropyridine Ca channel blocker, in the core tablet were prepared by dry coating with different polyethylene oxide-polyethylene glycol mixtures. Each formulation showed a clear lag period before nifedipine release initiation, followed by sustained drug release lasting up to 24 h. The lag time of nifedipine release increased as the amount of polyethylene oxide in the outer layer increased. To investigate the applicability of such CC-tablets for chronopharmacotherapy, the pharmacokinetics of CC-1 and CC-2 tablets, with different in vitro lag times before drug release, were compared with the pharmacokinetics of a sustained-release (SR) tablet in dogs. These results indicate that a CC-tablet with a lag time before drug release is a potentially useful formulation for chronopharmacotherapy that can control the time and duration of plasma drug concentration better than existing SR technologies.

Ishibashi *et al., (1998)* Development of a new capsule-type colon specific drug delivery system in healthy volunteers. And its Scintigraphic evaluation. Colonic drug delivery is intended for local or systemic therapies. The lack of predictive in vitro or animal model leads to considerable time delays in colonic product development. The objective of this scintigraphic study was to provide "proof of concept" for a novel capsule-type colonic delivery system (Colon-

Targeted Delivery Capsule) in healthy volunteers. The human data validates the design concept behind the release mechanism, in that capsule disintegration, and hence drug release, did not start until 5 h after gastric emptying, irrespective of whether the product was administered to fasted or fed subjects. However, the potential for prolonged gastric residence for large enteric coated products intended for intestinal targeting was also observed; overall, the study provides a focus for subsequent product development and highlights the role of scintigraphy in dynamically visualizing the drug delivery process.

SharmaS, PawarA (2006) A multiparticulate floating-pulsatile drug elivery system was developed using porous calcium silicate (Florite RE) and sodium alginate, for time and site specific drug release of meloxicam. Drug adsorbed FLR powder was used to prepare calcium alginate beads by ionotropic gelation method, using 3(2) factorial design. Entrapment efficiency of different formulations varied from 70% to 94%. Formulations show a lag period ranging from 1.9 to 7.8 h in acidic medium followed by rapid release of meloxicam in simulated intestinal fluid USP, without enzymes (SIF). Complete drug release in SIF occurred in less than 1h from the formulations. The size of beads varied from 2.0 to 2.7 mm for different batches. Floating time was controlled by density of beads and hydrophobic character of drug. A pulsatile release of meloxicam was demonstrated by a simple drug delivery system which could be useful in chronopharmacotherapy of rheumatoid arthritis.

Andrea *et al.,*(2008) evaluated the use of hydrophilic polymers in Oral pulsatile delivery systems based on swellable hydrophilic polymers Upon contact with aqueous fluids, swellable hydrophilic polymers undergo typical chain relaxation phenomena that coincide with a glassy–rubbery transition. In the rubbery phase,

these polymers may be subject to swelling, dissolution and erosion processes or, alternatively, form an enduring gel barrier when cross-linked networks (hydrogels) are dealt with. Because of the peculiar hydration and biocompatibility properties, such materials are widely exploited in the pharmaceutical field, particularly as far as hydrophilic cellulose derivatives are concerned. In most cases, water-swellable polymers play a key role in the overall delivery mechanism after being activated by physiological media. Based on these premises, the aim of the present review is to survey the main oral pulsatile delivery systems, for which swelling, dissolution and/or erosion of hydrophilic polymers are primarily involved in the control of release.

Bruno *et al.,* (1992) given an modelling of mexiletine and hydroxy-methyl-mexiletine data after single- and multiple-dose administration of a sustained-release mexiletine formulation. The pharmacokinetics of mexiletine and its metabolite hydroxy-methyl-mexiletine have been investigated following single-dose and during multiple-dose administration of a sustained-release form of mexiletine to six post-myocardial infarct patients. Comparison of single-dose and washout pharmacokinetics, after short-term multiple-dose administration, showed significant ($p < 0.005$), The fraction of mexiletine metabolized to hydroxy-methyl-mexiletine was lower for multiple-dose administration (about 18 per cent) than for the single dose (about 42 per cent). The hydroxy-methyl-mexiletine elimination rate constant was about four times that of mexiletine. Mexiletine clearance could be accounted for by other metabolic pathways. In one patient, hydroxy-methyl-mexiletine was undetectable even during multiple-dose administration, despite a significant increase in mexiletine clearance. However, the observed changes in

mexiletine disposition had no therapeutic implications and active plasma levels were achieved by the third day of administration and maintained in the therapeutic range (0.75 to 2 micrograms ml-1) in all patients after a twice daily dosage regimen.

Holt *et al.,* (1983) evaluated the Absorption and antiarrhythmic efficacy of sustained-release mexiletine. Absorption of the antiarrhythmic agent mexiletine from conventional capsules (200 mg) and two sustained-release formulations (360 and 432 mg) was studied in four healthy volunteer subjects, and use of the 360-mg preparation was studied in nine patients who had been using conventional capsules. In the four volunteers, acute dosage with the 432-mg preparation produced a markedly lower peak mexiletine concentration and fewer side effects than did two 200-mg capsules. Chronic dosing in two volunteers, which indicated that the 360-mg preparation produced fewer side effects and lower predose and peak plasma mexiletine concentrations than did the 432-mg preparation, suggested the use of equivalent doses of the 360-mg preparation in the nine patients who had been using 100-, 200-, or 250-mg preparations. The arrhythmia control produced by the slow-releasepreparation, as measured by 24-hour ECGs, was comparable to that produced by the conventional forms of mexiletine; gastrointestinal side effects were less marked when patients took the slow-release preparation, despite higher mean predose plasma mexiletine concentrations associated with use of the 360-mg preparation. Reduced frequency of daily dosage as well as patient acceptance is clinical advantages of the slow-releasepreparation.

3. AIM AND PLAN OF WORK

Aim and Objectives of the study:

The aim of the present work was formulation and *in-vitro* evaluation of *Mexiletine hydrochloride* 200mg timed- release capsules. Which release the drug at different time intervals in the GI tract

Objective of the work is to formulate timed release dosage form by adopting wet granulation method using synthetic polymers (HPMCE15), Croscormellose sodium and Eudragit L 100 at different ratios.

Mexiletine Hydrochloride was selected as a drug due to its low biological half life (A.J.cammn 1990) it requires frequent administration, hence timed release dosage form are formulated to reduce the dosing frequency thereby improving patient compliance.

1. To develop the timed release dosage form of the drug.

2. To perform drug: excipient compatibility studies.

3. To determine the drug content of the different granules of various dosage form.

4. To evaluate parameters such as morphology of the granules, particle size.

5. To reduce the systemic side effects, and to improve the patient compliance. It is delivered through timed-release dosage form.

6. To conduct the *in vitro* release studies for the dosage form.

In case of chronic treatment, where the drug is given in sustained release dosage form, continuous exposure of the drug to body may lead to adverse effects.

In case of *Mexiletine hydrochloride,* it is advised to divide the daily dose of 600-800mg into three does which are given at different time intervals. This is done to reduce the adverse effect as well as it has been reported that clinical outcomes are better when three divided doses are given.

Hence a timed-release dosage form of *mexiletine hydrochloride* will be investigated to deliver the doses at different time intervals in a pulsatile manner. Instead of taking three doses at three different time intervals per day, the patient will have to take two timed release capsule leading to better patient compliance.

PLAN OF WORK

Preformulation studies:

- Identification of pure drug:
- Melting point determination
- UV Spectroscopy
- To perform experimental methods
- To perform analytical methods

Preparation of timed release drug formulation of *Mexiletine hydrochloride* by wet granulation methods using polymers

Evaluation of granules

- Micromeritic properties
- Angle of repose
- Bulk density
- Tapped density
- Compressibility index
- Hausner's ratio
- Drug content uniformity
- Drug polymer interaction

FTIR to study drug polymer interaction

***In-vitro* dissolution studies:**

- Higuchi's Release model
- Korsmeyer and Peppas Release model:
- Zero Order Release Rate Kinetics:

Accelerated stability study:

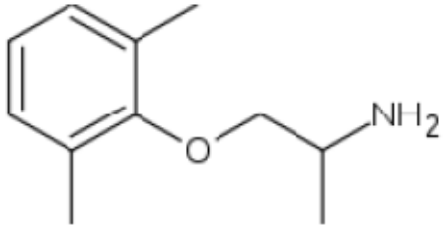
Stability studies for the optimized formulation were carried out at 40±2˚c/75±5%RH

4. MATERIALS AND METHODS

4.1 Drug profile

Drug name : Mexiletine hydrochloride

Structure :



IUPAC name : 2(2-amino propoxy) 1, 3-dimethyl benzene.

Chemical name : 1-menthyl-2(2, 6-xylyoxy) ethylamine Hydrochloride.

Molecular formula : $C_{11}H_{17}NO$

Mol.wt (MW) : 215.73.

Solubility : Freely Soluble in water and alcohol.

Category : Anti-arrhythmic agent.

Storage : 2 to 4^{o}C.

Melting point : 203-205^{o}C.

Half life (Hr) : 10-12hrs.

Indications : For the treatment of ventricular tachycardia and Symptomatic premature ventricular beats and prevention of ventricular fibrillation. Mexiletine hydrochloride is an anti-arrhythmic drug for the treatment of ventricular tachycardia and symptomatic premature ventricular beats, and prevention of ventricular fibrillation.

(Drug bank 2005)

Clinical pharmacology:

Mechanism of action:

Mexiletine structure is similar to local anesthetic drugs like lignocaine.The drug is rapidly absorbed in the GI tract and also has a longer duration of action. It inhibits the Inward sodium current required for the initation and conduction of impulses, thus reducing the rate of rise of the action potential, phase zero. Mexiletine decrease the effective refractory period (ERP) in purkinje fibers in the heart. It is well absorbed oral bioavailability from the GI tract.

Pharmacokinetics:

Mexiletine is almost completely absorbed orally, 90% metabolized in liver and excreted in urine. Plasma is $t_{1/2}$ 9-12 hrs.(Tripati 514)

4.2 EXCIPIENTS DATA:

4.2.1 HYDROXY PROPYL METHYL CELLULOSE (HPMC):

Nonproprietary Name

BP : Hypromellose

JP : Hydroxypropylmethylcellulose

PhEur : Hypromellousm

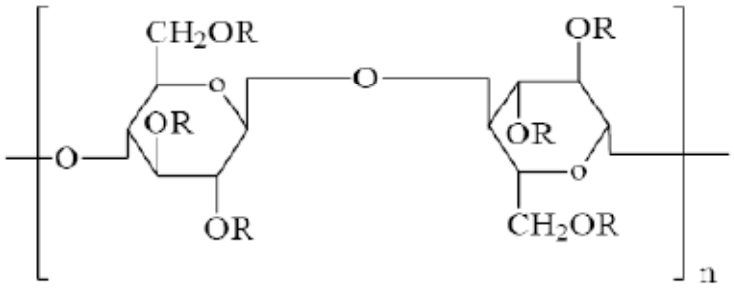
USP : Hypromellose

Synonym : Benecet MHPC, cellulose, hydroxyl propyl methyl ether,

E464; hydroxypropyl methylcellulose; HPMC: Methocel; methylcsllulose propylene

Glycol ether; methyl hydroxypropylcellulso; Metolose; pharmacist, spectracel 6, Spectracel 15, Tylopur.(Hogan 1989)

Structure



Where R is H, CH_3or [CH_3CH (OH) CH_2]

Chemical name : Cellulose, 2-hydroxy propyl methyl ether

Molecular weight : 10000-150000

Description : It is an odourless and tasteless, white or creamy white coloured fibrous power.

Moisture content : Hypromellose absorbs moisture from the atmosphere; the amount of water absorbed depends upon the intial moisture content and the temperature and relative humidity of the surrounding air.

Solubility : It is soluble in cold water; it is practically insoluble in ethanol (95 %) and ether.

Viscosity : Typical viscosity values for 2 % (w/v) aqueous solutions of HPMC viscosities measured at 20^{o}c.

Functional Category

HPMC is serves as a coating agent, film-former, rate-controlling polymer for sustained release, stabilizing agent, tablet binder and viscosity-increasing agent.

Safety

Hydroxy propyl methylcellulose is regarded as a nontoxic and nonirritant material.

Stability : It is a stable material, although it is hygroscopic after drying.

Storage Conditions: It should be stored in a well-closed container, in a cool, dry place.

Incompatibilities : HPMC is incompatible with some oxidizing agents. Since it is nonionic, hypromellose will not complex with metallic salts or ionic organics to form insoluble precipitates.

Applications in pharmaceutical technology

HMPC is widely used in oral and topical pharmaceutical formulations.

- HPMC is primarily used as a tablet binding in film coating, and as an extended release tablet matrix.
- HMPC is also used as a suspending and thickening agent for topical formulations, particularly ophthalmic preparations.
- As a protective colloid, it can prevent droplets and particles from coalescing or agglomerating, thus inhibiting the formation of sediments.
- In addition, HPMC is used in the manufacture of capsules, as an adhesive in plastic bandages, and as a wetting agent for hard contact lenses.

Table 4.2.1 Viscosity grades and applications:

Grade	Viscosity	Application
E5	5	Film Coating, Granulating agent
E15	15	Film Coating, Granulating agent, Suspending agent.
E50	50	Film coating, Granulating agent
E4M	4000	Sustained release, Medicated gel, Thickening agent.

4.2.2 LACTOSE:

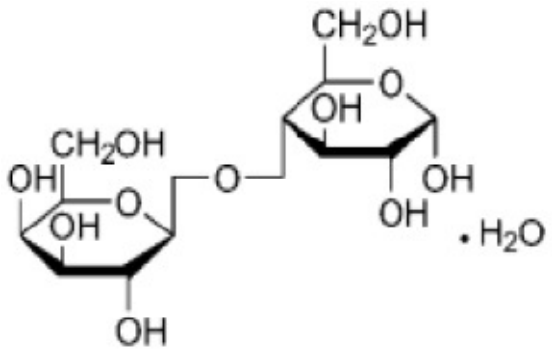
Synonyms Fast-Flo, 4-(β-D-galactosido)-D-glucose, Lactochem, Microtose Milksugar Pharmatose, Saccharumlactis, Tablettose, Zeparox.(Raymond *et.al,*2009)

Chemical Name : O-β-D-Galactopyranosy1-(1→4)-a-D-glucopyranose monohydrate

Empirical Formula : $C_{12}H_{22}O_{11}H_2O$

Molecular Weight : 360.31

Structural Formula :



Functional Category

Binding agent, diluents for dry-powder inhalers, tablet binder, tablet and capsule diluents.

Description

In the solid state, lactose appears as various isomeric forms, depending on the crystallization and drying conditions, i.e. ∝-lactose monohydrate and β-lactose anhydrous. Lactose occurs as white to off-white crystalline particles or powder. Lactose is odorless and slightly sweet-tasting; α-lactose is approximately 20% as sweet as sucrose, while β-lactose is 40% as sweet.

Safety

Lactose is widely used in pharmaceutical formulations as a diluents and filler-binder in Oral capsule and tablet formulations. It may also be used in intravenous injections. Adverse reactions to lactose are largely are due to lactose intolerance, which occurs in Individuals with a deficiency of the intestinal enzyme lactase, and is associated with Oral ingestion of amounts well over those in solid dosage forms.

Storage Conditions

Lactose anhydrous should be stored in a well-closed container in a cool, dry place.

Incompatibilities

A Millard-type condensation reaction is likely to occur between lactose and compounds with a primary amine group to form brown, or yellow-brown-colored products. Lactose is also incompatible with amino phenyl-line, amphetamines, and lisinop.

Applications in pharmaceutical technology

- Lactose is widely used as filler or diluents in tablets and capsules.
- Lactose is also used as a diluents in dry-powder inhalation.
- It is also used in lyophilized products, where lactose is added to freeze-dried solutions to increase plug size and aid cohesion.
- Lactose is also used in combination with sucrose (approximately 1:3) to prepare sugar-coating solutions.

4.2.3. CROSCARMELLOSE SODIUM (CCS):

Non proprietary names

BP : Croscarmellose Sodium

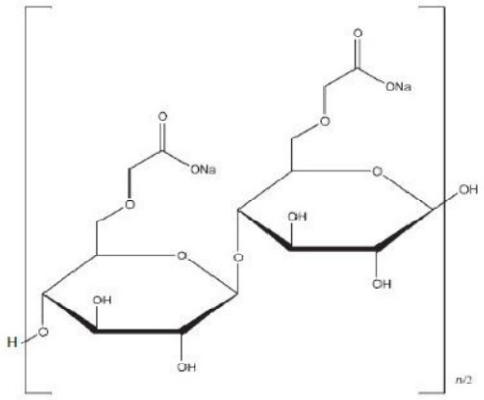
JP : Croscarmellose Sodium

PhEur : Croscarmellose Sodium

USP-NF : Croscarmellose Sodium

Synonyms: Carmellosumnatricumconexum; crosslinkedcarboxymethyl cellulose Sodium; Explocel; modified cellulose gum.(Raymond *et.al,*2009)

Structure



Chemical name : Cellulose, carboxymethyl ether.

Functional Category : Tablet and capsule disintegrant

Description : Croscarmellose sodium occurs as an odorless, white or grayishwhite powder.

Solubility : Insoluble in water. Practically insoluble in acetone, ethanol and toluene.

Stability : Croscarmellose sodium is stable though hygroscopic material.

Storage : The bulk material should be stored in a well-closed container in a cool, dry place.

Applications in pharmaceutical technology

In tablet formulations, croscarmellose sodium may be used in both direct-compression and wet-granulation processes.

When used in wet granulations, the croscarmellose sodium should be added in both the wet and dry stages of the process (intra- and extragranulary) so that the wicking and swelling ability of the disintegrant is best utilized.

4.2.4 MAGNESIUM STERATE:

Nonproprietary Names

BP : Magnesium Stearate

JP : Magnesium Stearate

PhEur : Magnesium Stearate

USP-NF : Magnesium Stearate

Synonyms

Dibasic magnesiumstearate, magnesium distearate, magnesistearas, magnesium octadecanoate, octadecanoic acid, magnesium salt, stearic acid.(Raymond *et.al,*2009).

Chemical Name **:** Octadecanoic acid magnesium salt.

Structural formula **:** $[CH_3 (CH_2)_{16}COO]_2Mg$

Functional Category **:** Tablet and capsule lubricant

Description: Magnesium stearate is a very fine, light white, precipitated or milled, impalpable powder of low bulk density, having a faint odor of stearic acid and a characteristic taste. The powder is greasy to the touch and readily adheres to the skin.

Solubility: Practically insoluble in ethanol, ethanol (95%), ether and water; slightly soluble in warm benzene and warm ethanol.

Stability & Storage Conditions

Magnesium stearate is stable and should be stored in a well-closed container in a cool, dry place.

Applications in pharmaceutical technology

It is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25% and 5.0% w/w. Magnesium stearate is widely used in cosmetics, foods, and pharmaceutical formulations. It is also used in barrier creams.

4.2.5 EUDRAGIT:

Nonproprietary names

BP : Methacrylic Acid-Methyl Methacrylate Copolymer

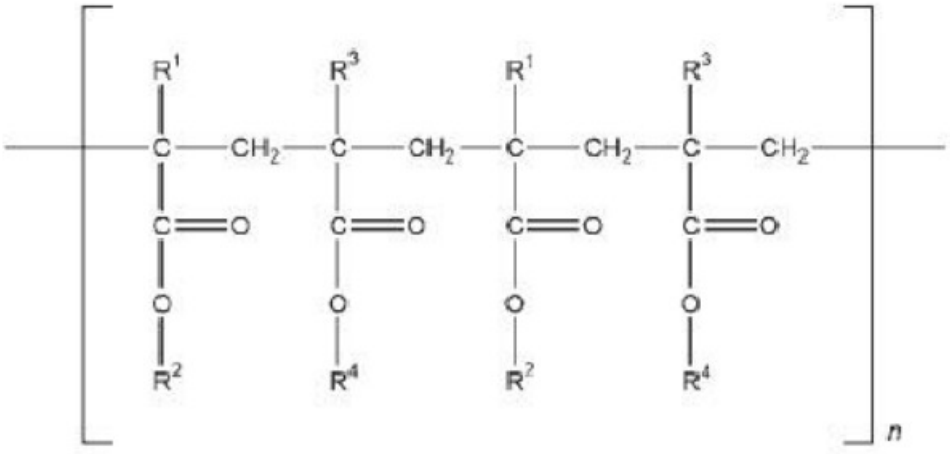
PhEur : Methacrylic Acid-Methyl Methacrylate Copolymer

USP-NF : Methacrylic Acid-Methyl Methacrylate Copolymer

Synonyms

Acryl-EZE; acidimethacrylici et ethylisacrylatispolymerisatum; acidimethacrylici et methylismethacrylatispolymerisatum; ammoniomethacrylatiscopolymerum; copolymerummethacrylatisbutylatibasicum; Eastacsryl; Eudragit; Kollicoat MAE; polymeric methacrylates.(Raymond *et.al,*2009)

Structure



For Eudragit L: R^1, R^3 = CH3, R^2 = H, R^4 = CH3.

Chemical name **:** Poly (methacrylic acid, methyl methacrylate)

Functional Category **:** Film-forming agent; tablet binder; tablet diluents.

Description: Eudragit L and S, also referred to as methacrylic acid copolymers in the USP32-NF27 monograph, are anionic copolymerization products of methacrylic acid and methyl methacrylate. That ratio of free carboxyl groups to the ester is approximately 1 :1 in Eudragit L (Type A) and approximately 1 : 2 in Eudragit S (Type B). Both polymers are readily soluble in neutral to weakly alkaline Conditions (pH 6-7).

Solubility: Eudragit L 100 is an enteric coated polymer. It is soluble in acetone, alcohols and intestinal fluid.

Stability: Dry powers are stable for at least 3 years if stored in a tightly closed container at less than 30°C.

Incompatibilities

Depending upon the ionic and physical properties of the polymer and solvent. For example, coagulation may be soluble electrolytes, pH changes, some organic solvents, and extremes of temperature. For example, dispersions of Eudragit L 30D, RL 30, L 100-55, and RS 30 D are incompatible with magnesium stearate.

Applications in pharmaceutical technology: Polymethacrylates are primarily used in oral capsule and tablet formulations as film-coating agents. Depending on the type of polymer used; Eudragit L is soluble at pH>6. Polymethacrylates are also used as binders in both aqueous and organic wet-granulation processes.

4.2.6 TALC:

Nonproprietary names

BP : Purified Talc

JP : Talc

PhEur : Talc

USP : Talc

Synonyms: Hydrous magnesium calcium silicate; hydrous magnesium silicate; Imperial; Luzenac Pharma; magnesium hydrogen metasilicate; MagsilOsmanthus; Magsil Star; powdered talc; purified French chalk; Pure French talc; soapstone; steatite; Superiore; talcum. (Raymond *et.al,*2009)

Functional Category: Ant caking agent; glidant; tablet and capsule diluents; tablet and capsule lubricant.

Description: Talc is a very fine, white to grayish-white, odorless, impalpable, crystalline powder. It adheres readily to the skin and is soft to the touch and free from grittiness.

Solubility: Practically insoluble in dilute acids and alkalis, organic solvents, and water.

Stability and Storage Conditions: Talc is a stable material and may be sterilized by heating at 160℃ for not less than 1 hour. It may also be sterilized by exposure to ethylene oxide or gamma irradiation. Talc should be stored in a well-closed container in a cool, dry place.

Incompatibilities: Incompatible with quaternary ammonium compounds.

Applications in pharmaceutical technology: Talc was once widely used in oral solid dosage formulations as a lubricant and diluents, although today it is less commonly used. However, it is widely used as a dissolution retardant in the development of controlled-release products.

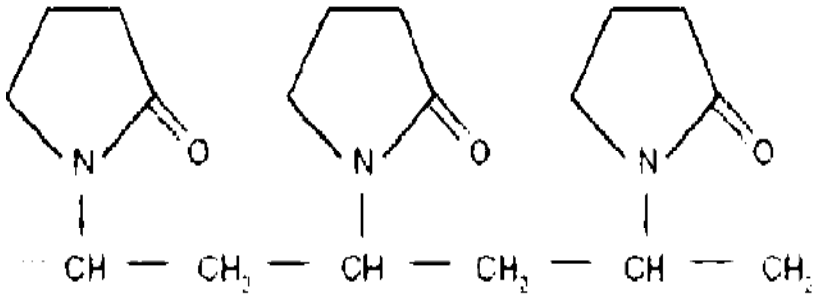
4.2.7 POLYVINYL PYRROLIDINE:

Nonproprietary names

BP : Polyvinyl pyrrolidine

USP : Polyvinyl pyrrolidine

Structure



Chemical name

Poly (1-(2-oxo-1-pyrrolidinyl)ethylen) 1-ethenyl-2-pyrrolidon homopolymer 1-vinyl-2-pyrrolinon-polymer copovidone.(Heburtus and Ansul 2008)

Empirical formula : $(C_6H_9NO)_n$

Molecular weight : 44,000-54,000

Functional category : Binding agent

Solubility : Soluble in water and hydrophilic, hydrophobic solvents

Description : White to yellow-white powder

Storage : It should be stored in air tight Containers.

Applications is pharmaceutical technology :

Numerous applications in medicine, cosmetics.

4.3 Materials used:

Table 4.3.1-List of materials used:

Sl. No.	Excipients	Vendor
1.	Maxiletine hydrochloride	Sigma Aldrich, China
2.	Lactose	SD fine chemicals, Mumbai
3.	Cross carmellose sodium	Waksman SlemanPvt Ltd, Atp
4.	Poly vinyl pyrrolidine	Waksman SlemanPvt Ltd, Atp
5.	HPMC E15	Waksman SlemanPvt Ltd, Atp
6.	Eudragit L 100	Waksman SlemanPvt Ltd, Atp
7.	Magnesium stearate	Lobachemie, Mumbai

Equipments used

Table 4.3.2: List of equipments used in the present work is as follows:

S.NO	Instruments	Source
1.	Digital Electronic balance AX200	Shimadzu corporation, Japan
2.	Digital pH meter	Digisum electronics system, Hyderapad.
3.	UV/Visible spectrophotometer, 1700	Shimadzu corporation, Japan
4.	Digital Weighing Balance	Ohaus, SP:202, USA
5.	Dissolution apparatus	Labindia, Mumbai.
6.	Hot air oven	Labline, Cochian
7.	FTIR spectrophotometer	Shimadzu Corporation, Japan
8.	DSC	SDT Q600 V8.2 build 100

4.4. METHODOLOGY:

4.4.1.PREFORMULATION STUDIES:

Preformulation is the first step in the rationale development of dosage forms of a drug substance. It can be defined as an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. The overall objective of preformulation testing is to generate information useful to formulator in developing stable and bioavailable dosage forms which can be mass-produced.

4.4.1.1. Identification of pure drug: Identification of *Mexiletine HC1* was carried out by Infrared Absorption Spectrophotometry.

4.4.1.2. Melting point determination: Melting point of *Mexiletine HC1* was determined by Open capillary method.

4.4.1.3 UV Spectroscopy:

The first step in preformulation is to establish a simple analytical method so that all future measurements can be quantitative. Most drugs absorb light in the ultraviolet wavelengths (200-400nm), since they are generally aromatic or contain double bonds.

Preparation of the sample for UV analysis

10mg of Mexiletine HC1 was accurately weighed on a microbalance and dissolved in 10ml water (=1000mcg/ml). Water is UV transparent and a good solvent for most polar and non-polar drugs. 1ml of this solution was diluted with 100ml of pH 1.2, pH6.8 and pH7.4 (=10mcg/ml) in separate volumetric flask and scanned on a

UV scanner between 200 to 400nm. The maxima obtained in the graph were considered as λ_{max} for the pure drug at respective buffers.

4.5 Calibration curves

Experimental methods

Sodium hydroxide solution, 0.2M: Eight grams of sodium hydroxide was dissolved in distilled water and diluted to 1000 ml with distilled water.

Potassium dihydrogen phosphate solution, 0.2 M: Potassium dihydrogen phosphate (27.218 g) was dissolved in distilled water and diluted to 1000 ml.

Hydrochloric acid solution, 0.1 N: Concentrated hydrochloric (8.5 ml) acid was diluted with distilled water and volume was made up to 1000 ml with distilled water. pH (1.2) was adjusted with dilute hydrochloric acid.

Phosphate buffer solution, pH 6.8: Potassium dihydrogen phosphate, 250 ml of 0.2 M, was placed in a 1000 ml volumetric flask, 112 ml of 0.2 M sodium hydroxide was added and then volume was adjusted with distilled water up to 1000 ml. pH was adjusted to 6.8 with dilute sodium hydroxide.

Phosphate buffer solution, pH 7.4: Potassium dihydrogenphosphate, 250 ml of 0.2M, was placed in a 1000 ml volumetric flask, 195.5 ml of 0.2M sodium hydroxide was added and then volume was adjusted with distilled water up to 1000 ml. pH was adjusted to 7.4 with dilute sodium hydroxide.

Analytical Methods

4.5.1 Preparation of calibration curve in water:

- An accurately weighted amount of Mexiletine HC1 equivalent to 100 mg was dissolved in small volume of water, in 100 ml volumetric flask and the volume was adjusted to 100 ml with water (stock I). Form stock I 5ml of solution is transferred to 50 ml volumetric flask (stock II). A series of standard solution containing Beer-Lambert's range of concentration from 5 to 2 µg/ml of Mexiletine HC1 were prepared from stock II and absorbance was measured at 262 nm spectrophotometrically against water buffer as blank.

4.5.2 Preparation of calibration curve in 1.2pH buffer:

- An accurately weighted amount of Mexiletine HC1 equivalent to 100 mg was dissolved in small volume of 1.2 buffer, in 100 ml volumetric flask and the volume was adjusted to 100 ml with 1.2 pH buffer (stock I). From stock I 5ml of solution is transferred to 50ml volumetric flask (stock II). A series of standard solution containing Beer-Lambert's range of concentration from 5 to 25µg/ml of Mexiletine HC1 were prepared from stock II and absorbance was measured at 262 nm spectrophotometrically against 1.2 pH buffer as blank.

4.5.3 Preparation of calibration curve in 7.4 pH buffer:

- An accurately weighed amount of Mexiletine HC1 equivalent to 100 mg was dissolved in small volume of buffer, in 100 ml volumetric flask and the volume was adjusted to 100 ml with 7.4 pH buffer (stock I). From stock I 5ml of solution is transferred to 50 ml volumetric flask (stock II). A series of standard solution containing Beer-Lambert's range of concentration from 5 to

25µg/ml of Mexiletine HC1 were prepared from stock II and absorbance was measured at 262 nm spectrophotometrically against 7.4 pH buffer as blank.

4.5.4 Preparation of calibration curve in 6.8 pH buffer:

- An accurately weighed amount of Mexiletine HC1 equivalent to 100 mg was dissolved in small volume of buffer, in 100 ml volumetric flask and the volume was adjusted to 100 ml with 6.8 pH buffer (stock I). From stock I 5ml of solution is transferred to 50 ml volumetric flask (stock II). A series of standard solution containing Beer-Lambert's range of concentration from 5 to 25µg/ml of Maxiletine HC1 were prepared from stock II and absorbance was measured at 262 nm spectrophotometrically against 6.8 pH buffer as blank,

4.6 Formulation development

Granules preparation:

Granules preparation is done by wet granulation method.

All the ingredients including drug and polymer, and excipients are weighed accurately according to formula mentioned in table 4.3 to 4.8

- All the ingredients are passed through a 24mesh sieve.
- Required quantity of drug, diluents and polymers are mixed thoroughly sufficient qty of binding agent polyvinyl pyrrolidine added slowly.
- After enough cohesiveness mass was obtained, the mass was sieve through a 16mesh sieve.
- The granules were dried at 50˚c for 45 minutes and were blended with magnesium stearate and talc

Table 4.3 Formulation of F1:

Formulation ingredients	**Granule composition-1**	**Granule composition-2**	**Granule composition-3**
	(pH1.2granules)	(pH 6.8granules)	(pH 7.4granules)
Mexiltine HC1	200mg	200mg	200mg
Lactose	40mg	-	-
Croscarmellose sodium	8mg	-	-
HPMC E15	-	20mg	-
Eudragit L 100	-	-	40mg
PVP K	1%	1%	1%
Magnesium stearate	5mg	5mg	5mg
Talc	5mg	5mg	5mg

Table 4.4 Formulation of F2:

Formulation ingredients	**Granule composition-1**	**Granule composition-2**	**Granule composition-3**
	(pH1.2granules)	(pH 6.8granules)	(pH 7.4granules)
Mexiltine HC1	200mg	200mg	200mg
Lactose	40mg	-	-
Croscarmellose sodium	8mg	-	-
HPMC E15	-	25mg	-
Eudragit L 100	-	-	60mg
PVP K	1%	1%	1%
Magnesium stearate	5mg	5mg	5mg
Talc	5mg	5mg	5mg

Table 4.5 Formulation of F3:

Formulation ingredients	**Granule composition-1**	**Granule composition-2**	**Granule composition-3**
	(pH1.2granules)	(pH 6.8granules)	(pH 7.4granules)
Mexiltine HC1	200mg	200mg	200mg
Lactose	40mg	-	-
Croscarmellose sodium	8mg	-	-
HPMC E15	-	30mg	-
Eudragit L 100	-	-	60mg
PVP K	1%	1%	1%
Magnesium stearate	5mg	5mg	5mg
Talc	5mg	5mg	5mg

Table 4.6 Formulation of F4:

Formulation ingredients	**Granule composition-1**	**Granule composition-2**	**Granule composition-3**
	(pH1.2granules)	(pH 6.8granules)	(pH 7.4granules)
Mexiltine HC1	200mg	200mg	200mg
Lactose	40mg	-	-
Croscarmellosesodium	8mg	-	-
HPMC E15	-	40mg	-
Eudragit L 100	-	-	60mg
PVP K	1%	1%	1%
Magnesium stearate	5mg	5mg	5mg
Talc	5mg	5mg	5mg

Table 4.7 Formulation of F5:

Formulation ingredients	**Granule composition-1**	**Granule composition-2**	**Granule composition-3**
	(pH1.2granules)	(pH 6.8granules)	(pH 7.4granules)
Mexiltine HC1	200mg	200mg	200mg
Lactose	40mg	-	-
Croscarmellose sodium	8mg	-	-
HPMC E15	-	60mg	-
Eudragit L 100	-	-	80mg
PVP K	1%	1%	1%
Magnesium stearate	5mg	5mg	5mg
Talc	5mg	5mg	5mg

Table 4.8 Formulation of F6:

Formulation ingredients	**Granule composition-1**	**Granule composition-2**	**Granule composition-3**
	(pH1.2granules)	(pH 6.8granules)	(pH 7.4granules)
Mexiltine HC1	200mg	200mg	200mg
Lactose	40mg	-	-
Croscarmellose sodium	8mg	-	-
HPMC E15	-	80mg	-
Eudragit L 100	-	-	1 00mg
PVP K	1%	1%	1%
Magnesium stearate	5mg	5mg	5mg
Talc	5mg	5mg	5mg

4.7 Evaluation of granules:

Prepared granules were evaluated for the following parameters(Ishikawa *et.al,*2000,Raghuram *et.al,*2003,Banker *et.al,*2001)

4.7.1 Angle of repose:

The angle of repose of the powder blend was determined by using funnel method. The accurately weighed powder was taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the powder. The diameter of the cone was measured and angle of repose was calculated by using the equation,

$$\theta = \tan^{-1} h/r$$

where,

h = height of the cone

r = radius of the cone

Flow properties for different values of angle of repose were given below.

Table-4.9 Flow property of powders according to angle of repose:

Angle of Repose (θ degrees)	Flow property
<25	Excellent
25 - 30	Good
30 - 40	Passable
>40	poor

4.7.2 Bulk density:

An amount of powder blend was introduced in a 100 ml measuring cylinder. Then the weight of powder blend was determined by subtracting the weight of empty measuring cylinder from final weight of measuring cylinder. The cylinder was allowed to fall onto a hard surface from a height of 2.5 cm at 2 sec intervals. The tapping was continued till no volume change noted. Bulk density was calculated by using the formula;

$$\text{Bulk density} = \frac{\text{Mass(gm)}}{\text{Volume(ml)}}$$

4.7.3 Tapped density:

Now this cylinder was put in the holder of USP tapped density apparatus where it was tapped at an average rate of 300 drops / minute, for 500 taps. After 500 taps volume of powder (V_0) was noted and again tapped for another 750 taps. This gave a new volume (V_f). If the difference between v_0 and v_f was more than 2% another 1250 taps are given repeatedly until the difference reduces to less than 2%.Tapped density was found out from following equation:

$$\text{Tapped density} = \frac{\text{Mass(gm)}}{\text{Tapped volume(ml)}} .$$

4.7.4 Compressibility index: The compressibility of the powder was determined by the Carr's compressibility index.

$$\text{Carr's index} = \frac{\text{Tapped bulk destiny} - \text{Loose bulk density}}{\text{Tapped volume (ml)}} \times 100$$

Table-4.10 Grating of powders according to Carr's index;

Compressibility index	Flow property
5-15	Excellent
12-16	Good
18-21	Fair to Passable
23-35	Poor
33-38	Very poor

4.7.6 Hausner's ratio:

Hausner's ratio is an indirect index of ease of measuring the powder flow. It is calculated by the following formula:

Hausner's ratio = Tapped density/ Bulk density

4.7.7 Drug content uniformity:

In 100 ml volumetric flask 750mg equivalent weight of granules are taken and dissolved in small quantity of water and the volume was made up to mark with pH 7.4 buffer and stirred for 12 hrs. After stirring the solution was filtered through whatman filter paper and from the filtrate dilutions were made and absorbance was measured spectrophotometrically at 262nm.

4.7.8 Drug polymer interaction:

FT-IR spectra of physical mixture of Mexiletine HC1+Lactose, Mexiletine HC1+Croscarmellose sodium, Mexiletine HC1+PVPk, Mexiletine HC1+Hpmc E15, mexilitine HC1+Eudragit L 100, Mexiletine HC1+Mg.Sterate were determined by using KBr pellet technique. Samples were scanned over the 4000-400cm^{-1}. Spectral

region at resolution of $4cm^{-1}$. These studies are done to ensure no interaction has been occurred between the drug and polymer.

4.8 Data analysis:

To analyse the mechanism of the drug release rate kinetics of the dosage form, the data obtained were graphed as

1) Cumulative percentage drug released v/s time(In-vitro drug release profile)
2) Cumulative percentage drug released v/s Square root of time (Higuchi's plots)
3) Log cumulative percentage drug remaining v/s time (First order release)
4) Log percentage drug released v/s log time (Peppas plots)(Nish demn 2003)

4.8.1 *In-vitro* release profile:

Dissolution studies were carried out by using USP Type-1 dissolution test apparatus (Basket) method. In order to simulate the pH changes along the GI tract, three dissolution media with pH 1.2, 7.4 and 6.8 were sequentially used referred to as sequential pH change method. When performing experiments, the pH 1.2 medium was first used for 2 hrs (since the average gastric emptying time is 2 hrs) then removed and the fresh pH 7.4 phosphate buffer saline (PBS) was added. After 6 hrs (average small intestinal transit time is 6 hrs) the medium was removed and fresh pH 6.8 dissolution medium was added for subsequent hrs. 900ml of the dissolution medium was used at each time. Rotation speed was 100 rpm and temperature was maintained at 37±0.5˚C five milliliters of dissolution media was withdrawn at predetermined time intervals and fresh dissolution media was replaced. The withdrawn samples were analyzed at 262 nm, by UV absorption spectroscopy.

4.8.2 Higuchi's Release model:

To study the Higuchi release kinetics, the release rate data were fitted to the following equation,

$$F = K.t^{1/2}$$

Where, 'F' is the amount of drug release,

'K' is the release rate constant, and

't' is the release time.

When the data is plotted as accumulative drug released versus square root of time, yields a straight line, indicating that the drug was released by diffusion mechanism. The slope is equal to 'K'.

4.8.3 Korsmeyer and Peppas Release model:

The release rate data were fitted to the following equation,

$$M_t/M\infty = K.t^n$$

Where, $M_t /M\infty$ is the fraction of drug release,

'K' is the release constant,

't' is the release time,

'n' is the diffusional exponent for the drug release that is dependent on the shape of the matrix dosage form.

When the data is plotted as Log of drug released versus Log time, yields a straight line with a slope equal to 'n' and the 'K' can be obtained from Y – intercept.

4.8.4 Zero Order Release Rate Kinetics:

To study the zero-order release kinetics the release rate date are fitted to the following equation.

$F = K.t$

Where 'F' is the fraction of drug release, 'K' is the release rate constant and 't' is the release time.

When the data is plotted as cumulative percent drug release versus time, if the plot is linear then the data obeys zero-order release kinetics, with a slope equal to K_0.

4.9 Accelerated stability studies:

Stability studies for the optimized formulation were carried out at 40±2˚c/75±5% RH for 6weeks. Stability studies were carried out using Thermo lab stability chamber. After 4weeks the optimized formulation was tested for physical appearance, drug content and DSC.

5. RESULTS AND DISCUSSION

5.1 PREFORMULATION STUDIES

5.1.1. Infrared spectroscopy:

The drug is identified as an mexiletine hydrochloride by the observation of peaks in the following region cm^{-1} 2590, 1616, 850, 1487, 1616 which is compared to the standard.

5.1.2 Melting point determination:

Melting point of Mexiletine HC1 was determined by **Open capillary method**. The results are tabulated in the table 5.1

Table 5.1 Melting point determination of Mexiletine hydrochloride

Trail1	Trail2	Trail3	Average
199°c	201°c	202°c	201°c

By comparing to the standard melting point which is found to be $203\text{-}205^0$c (drug bank DBOO379) it is more or less equal to the standard.

5.1.2 UV Spectroscopy:

UV scanning of the drug revealed that the drug had λmax of 262 nm in distilled water. Also, the IR spectrum was concordant with the reference spectrum of Mexiletine hydrochloride.

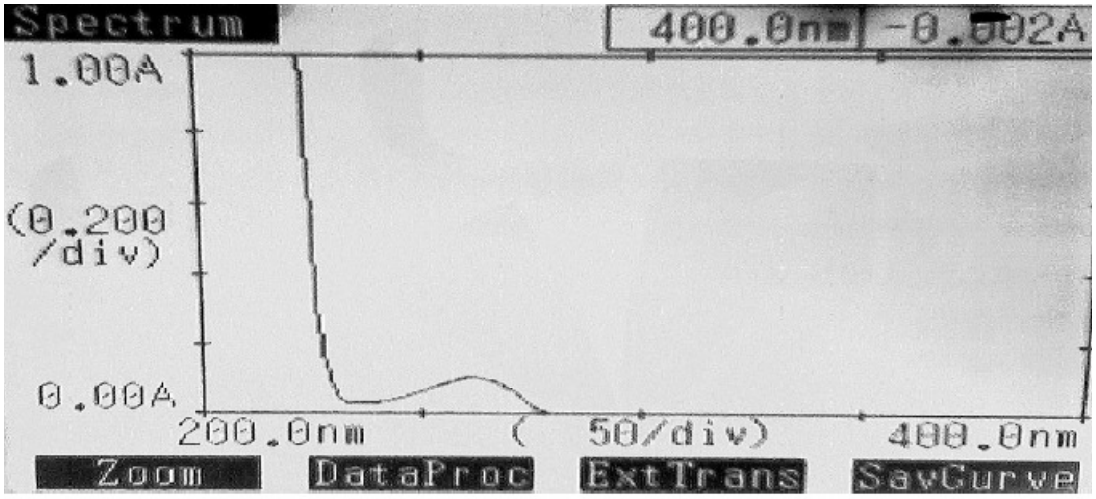


Fig 5.1 Wavelength scans of pure drug

5.2 Calibration curves

Calibration curve has been drawn using different solutions like water and buffers 1.2, 6.8, 7.4.and the graphs are under the following tables 5.2 to 5.5.

Table 5.2 Calibration data of Mexiletine hydrochloride in water:

Concentration (µg/ml)	Trail1	Trail2	Trail3	Absorbance ±SD*
0	0	0	0	0
5	0.061	0.060	0.078	0.066±0.010
10	0.118	0.117	0.128	0.122±0.005
15	0.171	0.178	0.181	0.176±0.005
20	0.206	0.240	0.246	0.230±0.021
25	0.280	0.300	0.298	0.292±0.007

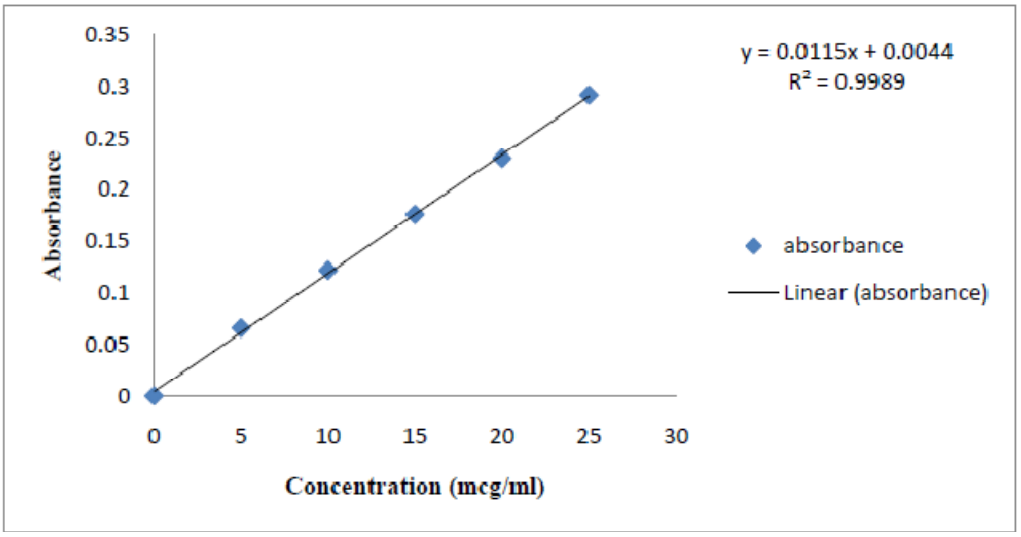


Fig 5.2 Calibration curve of Mexiletine HCl in Water

Table5.3 Calibration data of Mexiletine HC1 in 1.2 buffer

Concentration (µg/ml)	Trail1	Trail2	Trail3	Absorbance ±SD*
0	0	0	0	0
5	0.071	0.078	0.070	0.073±0.004
10	0.132	0.128	0.130	0.130±0.002
15	0.181	0.181	0.175	0.179±0.003
20	0.244	0.246	0.230	0.240±0.008
25	0.308	0.298	0.290	0.298±0.009

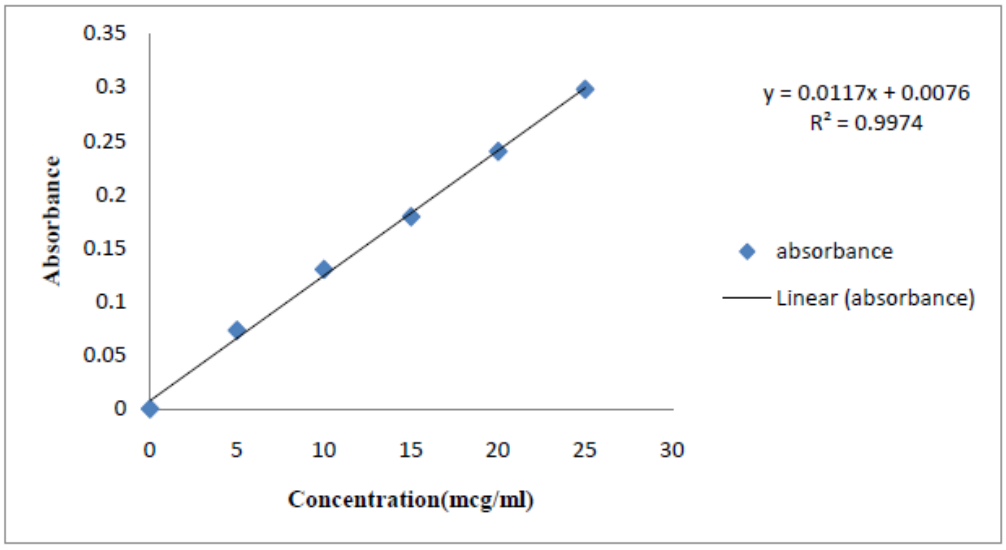


Fig 5.3 Calibration curve of Mexiletine HCl in 1.2 buffer

Table5.4 Calibration data of Mexiletine HC1 in 7.4 buffer

Concentration (µg/ml)	Trail1	Trail2	Trail3	Absorbance ±SD*
0	0	0	0	0
5	0.081	0.079	0.073	0.077±0.004
10	0.157	0.158	0.140	0.151±0.010
15	0.225	0.221	0.205	0.271±0.010
20	0.307	0.305	0.280	0.297±0.015
25	0.380	0.370	0.360	0.370±0.01

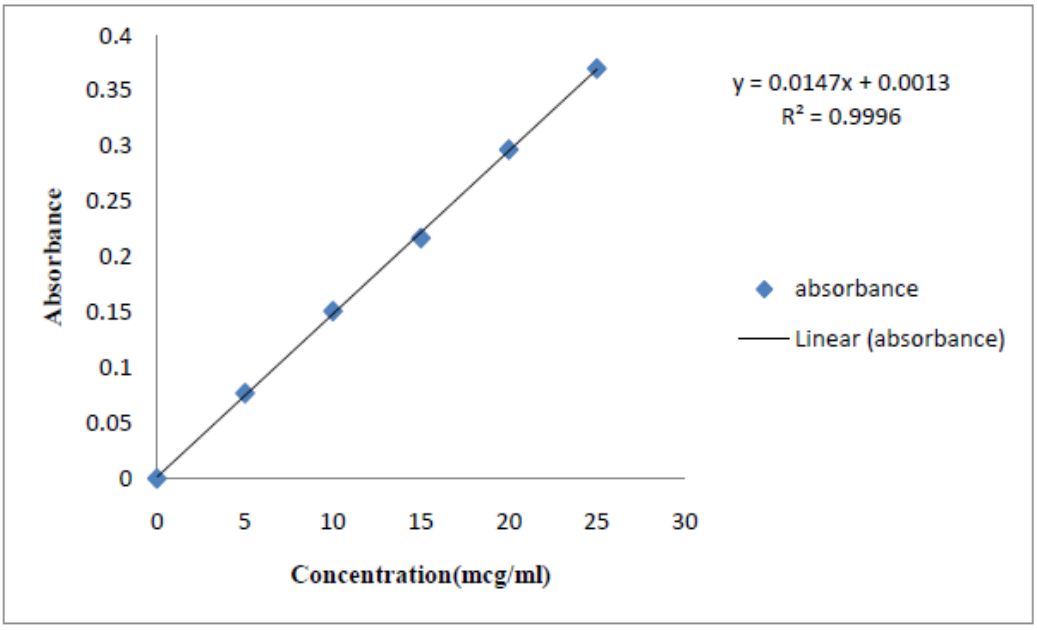


Fig 5.4 Calibration Curve of Mexiletine HCI in 7.4 buffer

Table 5.5 Calibration data of Mexiletine HC1 in 6.8 buffer

Concentration (µg/ml)	Trail1	Trail2	Trail3	Absorbance ±SD*
0	0	0	0	0
5	0.045	0.059	0.040	0.049±0.009
10	0.147	0.160	0.150	0.152±0.006
15	0.215	0.220	0.205	0.213±0.007
20	0.297	0.312	0.295	0.310±0.009
25	0.370	0.360	0.340	0.323±0.015

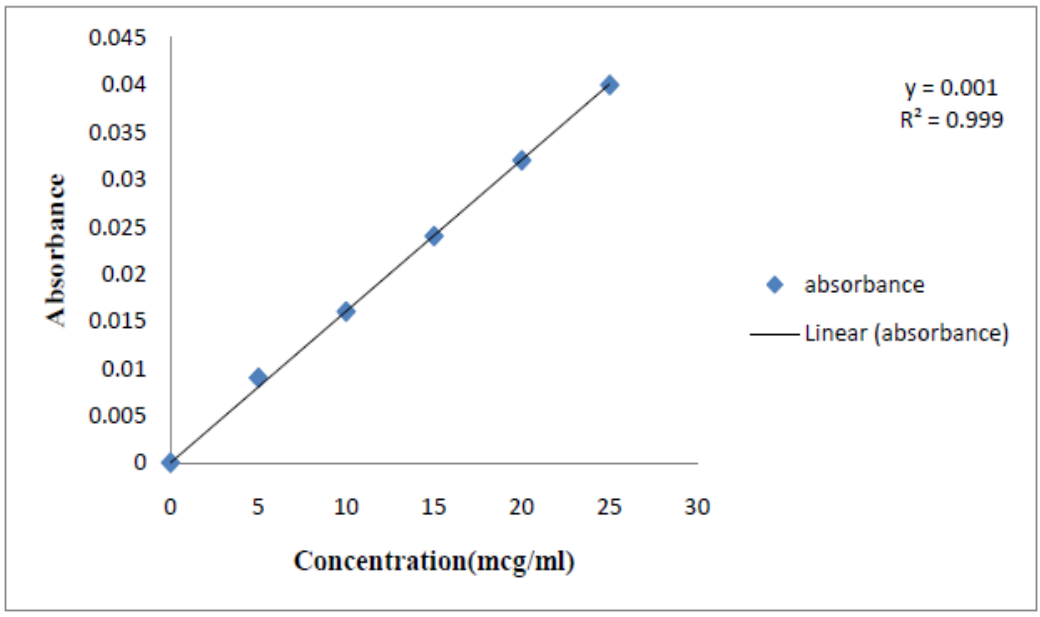


Fig 5.5 Calibration curve of Mexiletine HCl in 6.8 buffer

Discussion

From the standard curve of mexiletine hydrochloride,it was observed that the drug obeys Beer- Lambert's law in concentration range of 5-25µg/ml in water. The linear regression equation generated was used for the calculation of amount of drug.

5.3 Drug and polymer compatibility

Infrared analysis has been carried out to check the polymer compatibility with the polymers and the graph has been given in the following figures 5.6 to 5.12

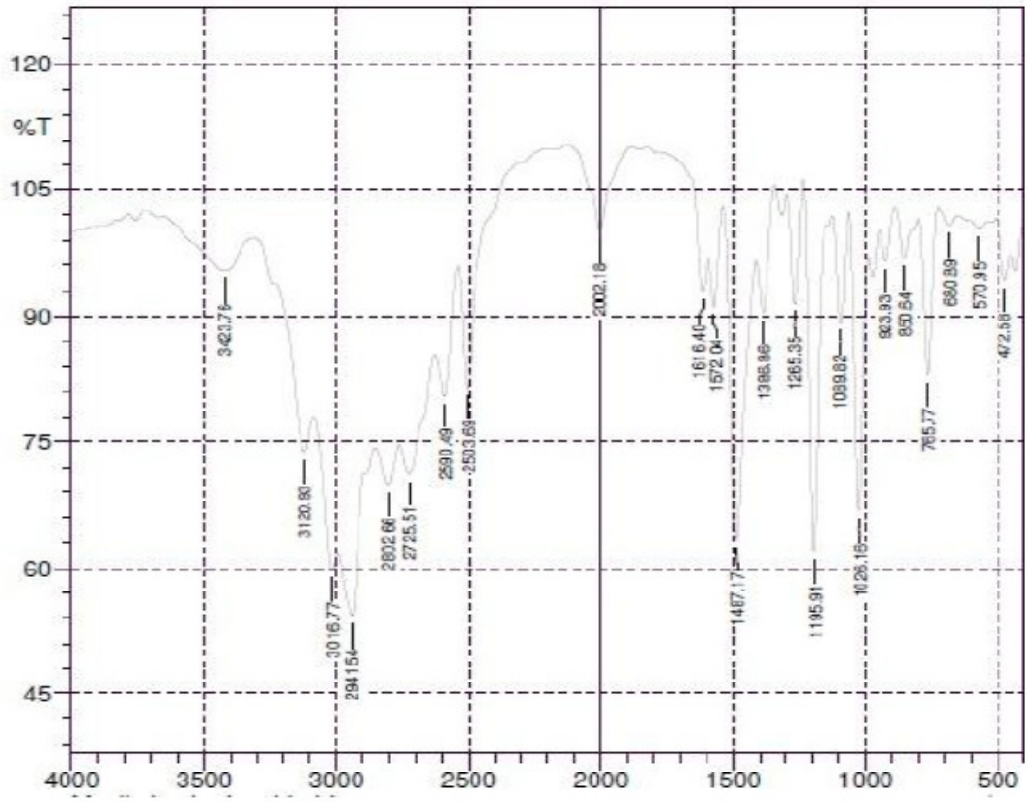


Fig 5.6 IR of pure drug

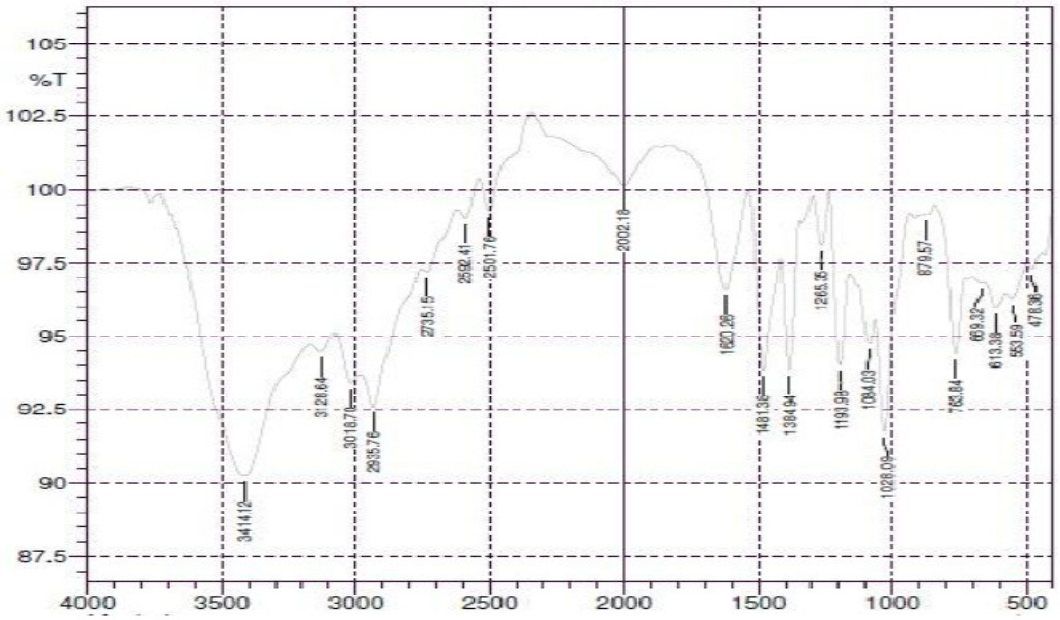


Fig 5.7 IR spectrum of Drug and Lactose

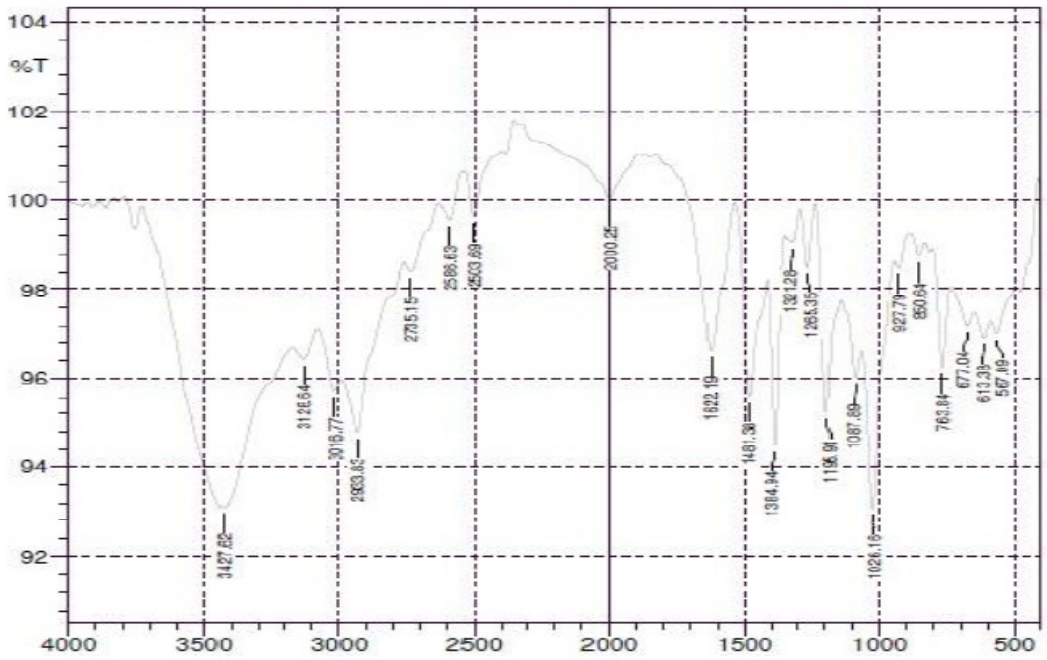


Fig 5.8 IR spectrum of Drug and Croscarmellose Sodium

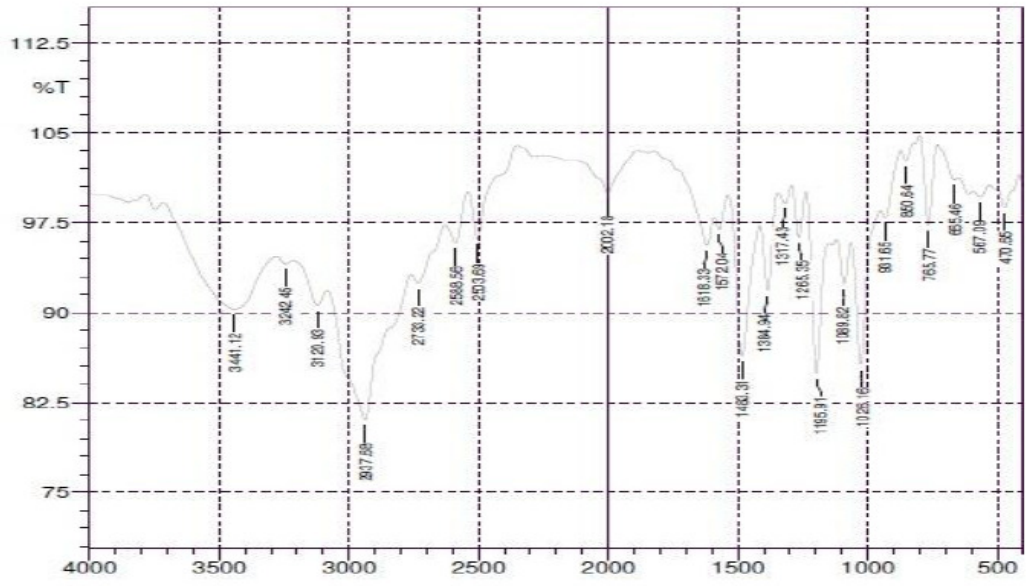


Fig 5.9. IR spectrum of Drug and HPMC

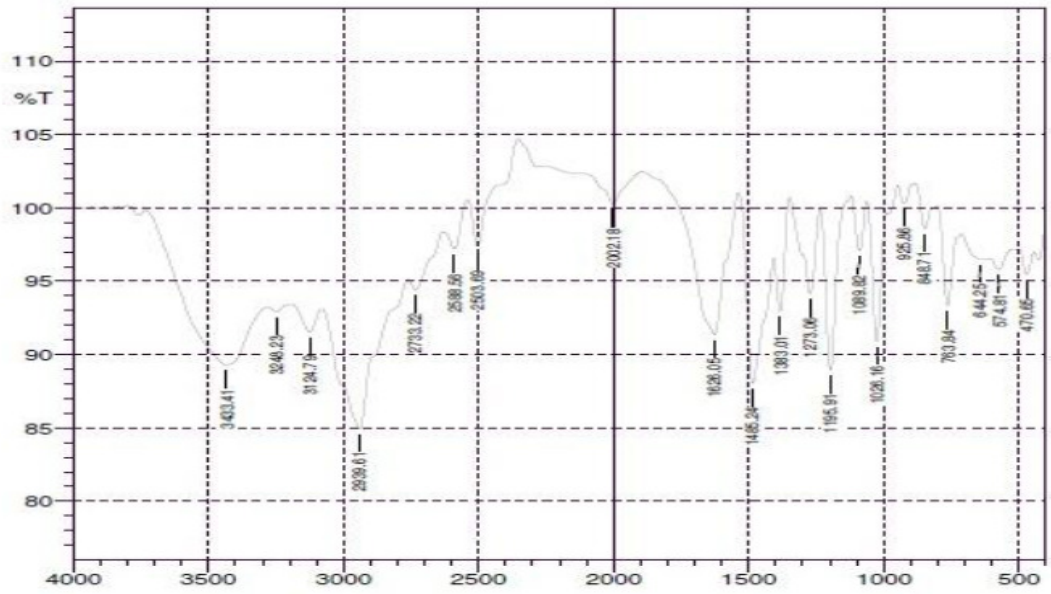


Fig 5.10 IR spectrum of Drug and PVP-K

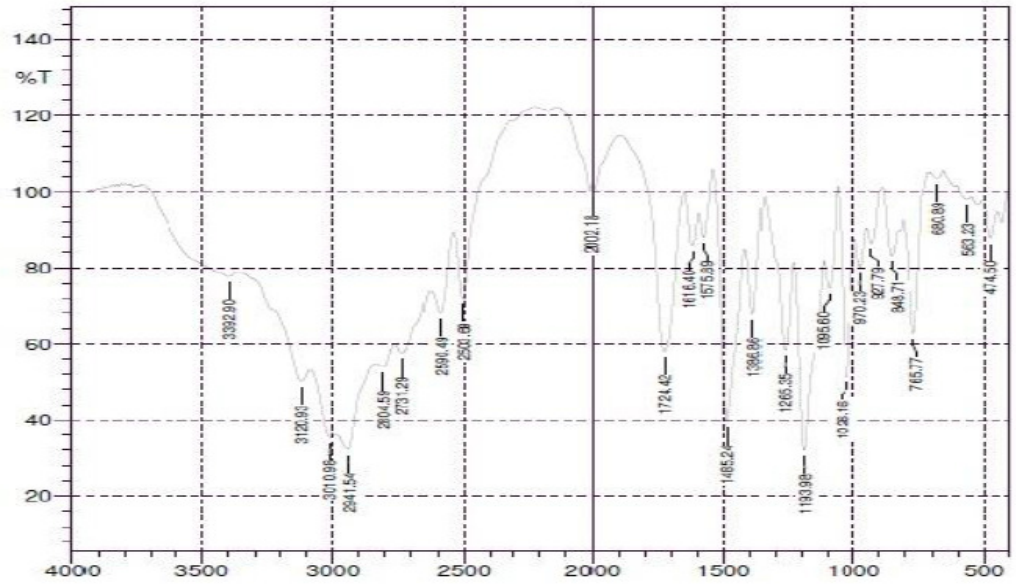


Fig 5.11 IR spectrum of Drug and Eudragit L 100

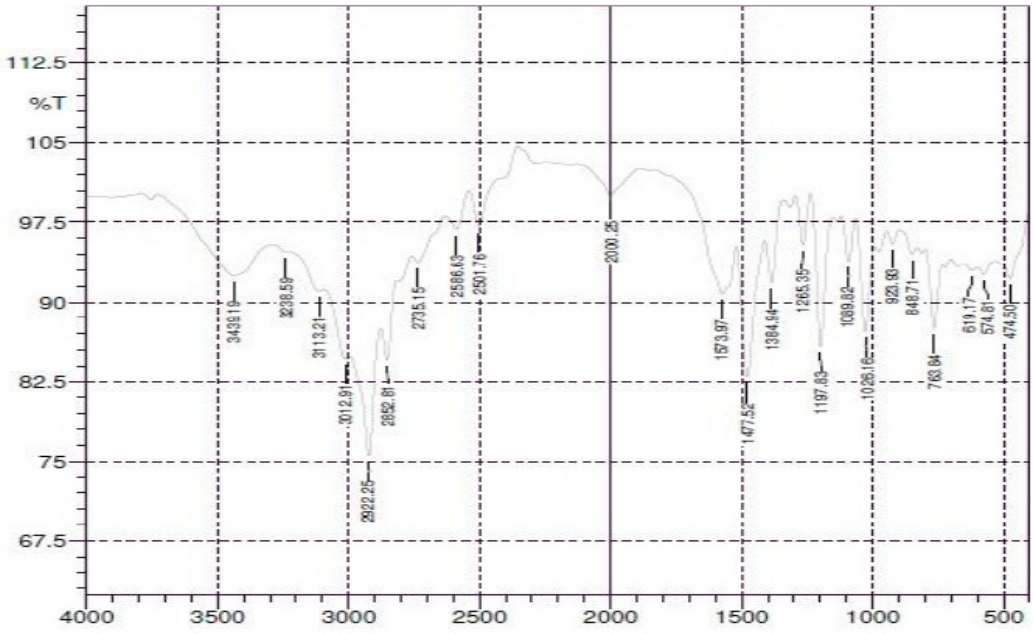


Fig 5.12 IR spectrum of Drug and magnesium stearate

Discussion:

Physical mixture of drug and polymer was characterized by FT-IR & DSC spectral analysis for any physical as chemical alteration of the drug characteristics. From the result it was concluded that there was no interference of the functional groups as the principal peaks of the mexiletine hydrochloride were found to be unaltered in the spectra of the drug-polymer physical mixture. And its wave number has been given in the following table.

Table 5.6 INTERPRATION DATA OF IR ANALYSIS:

Wave number	Functional group	Peaks observed in cm^{-1}	Drug	Polymers	Interaction
2450-2700	C-N	2590	YES	YES	NO
1250-1750	C=O	1616	YES	YES	NO
900-675	C-H	850	YES	YES	NO
1500-1400	C-C	1487	YES	YES	NO
1600-1700	N-H	1616	YES	YES	NO

5.4 Evaluation of granules

Six formulations of matrix granules were prepared (F1 to F6) by using various polymers such as HPMC E15 and Eudragit L100 in different ratios. The granules were prepared by wet granulation method.

Table 5.7 Evaluation parameters of Mexiletine HC1 matrix granules

Formulation	Angle of repose(degree)	Bulk density	Tapped density	Compressibility index	Hausner's ratio
F1	27.23°	0.596	0.748	18.45	1.289
F2	28.36°	0.623	0.736	17.95	1.245
F3	26.46°	0.601	0.740	18.98	1.356
F4	28.76°	0.612	0.750	18.36	1.225
F5	29.21°	0.589	0.725	18.65	1.198
F6	29.56°	0.623	0.745	18.24	1.244

Discussion:

- **Pre compression evaluation**

Carr's compressibility index was found to be less than 20% for all the formulations indicating that the powder is compressible. Bulk density and true densities were found to be <1 for all formulation powders. The result of Angle repose studies and Hausner's ratio indicated that, the powders of all the formulations have free flow and easily compressible.

5.4.1 Drug content uniformity:

In these all the formulations the percentage of drug release has been mentioned in the table 5.7

Table 5.8 Drug content uniformity of matrix granules

Formulation	% Cumulative drug release
F1	86.6%
F2	88.0%
F3	87.3%
F4	93.3%
F5	85.3%
F6	84.0%

The drug content uniformity was found to be 93.3 w/w%.

5.5 Post Compression evalution:

5.5.1 invitro release profile:

Table 5.9 Dissolution profile of formulation of F1

Time	absorbance	C in mcg	C in V Made up	C in D.M	Loss	CLA	CDR	%CDR	C%D Retained	Log %CD released	Log %CD Retained
5	0.063	5.72727	0.057273	51.545	0	0	51.54545	25.77273	74.227	1.41116	1.8705635
10	0.089	8.09091	0.080909	72.818	0.0573	0.057273	72.87545	36.43773	63.562	1.561551	1.8031994
20	0.095	8.63636	0.086364	77.727	0.0809	0.138182	77.86545	38.93273	61.067	1.590315	1.7858085
30	0.11	10	0.1	90	0.0864	0.224545	90.22455	45.11227	54.888	1.654295	1.7394752
40	0.114	10.3636	0.103636	93.182	0.1	0.324545	93.59727	46.79864	53.201	1.670233	1.7259228
50	0.12	10.9091	0.109091	98.182	0.1036	0.428182	98.61	49.305	50.695	1.692891	1.7049651
60	0.128	11.6364	0.116364	104.73	0.1091	0.537273	105.2645	52.63227	47.368	1.721252	1.6754825
120	0.132	12	0.12	108	0.1164	0.653636	108.6536	54.32682	45.673	1.735014	1.6596613
180	0.022	1.46667	0.014667	13.2	0	0	13.2	6.6	93.4	0.819544	1.9703469
240	0.024	1.6	0.016	14.4	0.0147	0.014667	14.41467	7.207333	92.793	0.857775	1.9675137
300	0.013	0.86667	0.008667	7.8	0.016	0.030667	7.830667	3.915333	96.085	0.592769	1.9826541
360	0.014	0.93333	0.009333	8.4	0.0087	0.039333	8.439333	4.219667	95.78	0.625278	1.9812763
420	0.02	1.33333	0.013333	12	0.0093	0.048667	12.04867	6.024333	93.976	0.779909	1.9730154
480	0.022	1.46667	0.014667	13.2	0.0133	0.062	13.262	6.024333	93.369	0.821579	1.9702027
540	0.002	2	0.02	18	0	0	18	9	91	0.954243	1.9590414
600	0.016	1	0.01	9	0.02	0.02	9.02	4.51	95.49	0.654177	1.9799579

Table 5.10 Dissolution profiles of formulation of F2

Time	Absorbance	Cin mcg	Cin V made up	Cin D.M	Loss	CLA	CDR	%CDR	C% D Retained	Log% CD Released	Log % CD Retained
5	0.056	5.09091	0.050909	45.81818	0	0	45.81818	22.90909	77.0909	1.36008	1.8870032
10	0.064	5.8181	0.058182	52.36364	0.050909	0.050909	52.41455	26.20727	73.7927	1.418422	1.8680136
20	10.088	8	0.08	72	0.05818	0.109091	72.10909	36.05455	63.9455	1.55696	1.8058097
30	0.11	10	0.1	90	0.08	0.18991	90.18909	45.09455	54.9055	1.654124	1.76396155
40	0.121	11	0.11	99	0.1	0.289091	99.28909	49.64455	50.3555	1.695872	1.7020465
50	0.13	11.8182	0.118182	106.3636	0.11	0.3990914	106.7627	53.38136	46.6186	1.72739	1.6685596
60	0.136	12.3636	0.1253636	111.2727	0.118182	0.517273	111.79	55.895	44.105	1.747373	1.6444878
120	0.1478	12.8182	0.128182	115.3636	0.123636	0.640909	116.0045	58.00227	41.9977	1.763445	1.6233258
180	0.09	6	0.06	54	0	0	54	27	73	1.43136	1.86332
240	0.085	5.66667	0.056667	51	0.06	0.06	51.06	25.53	74.47	1.407051	1.8719814
300	0.08	5.33333	0.053333	48	0.056667	0.116667	48.11667	24.05833	75.9417	1.396303	1.8820405
360	0.079	5.26667	0.052667	47.4	0.053333	0.17	47.57	23.785	76.215	1.376303	1.88204058
420	0.06	4	0.04	36	0.052667	0.222667	36.22267	18.11133	81.8887	1.25795	1.9132238
480	0.058	3.86667	0.038667	34.8	0.04	0.262667	35.06267	17.563133	82.4687	14.243815	1.916289
600	0.007	7	0.07	63	0.09	0.09	63.09	31.545	68.454	1.498931	1.8628467
660	0.006	6	0.06	54	0.07	0.16	54.16	27.08	72.92	10432649	1.8628467

Table 5.11 Dissolution profiles of formulation of F3

Time	Absorbance	CONC (mcg)	C in V made up	C in disso medium	Loss	CLA	CDR	%CDR	C%D Retained	Log% CD Released	Log %CD Retained
5	0.054	4.909091	0.04909091	44.18182	0	0	44.18182	22.09091	77.909	1.3442136	1.8915881
10	0.062	5.636364	0.05636364	50.72727	0.049091	0.049091	50.77636	25.38818	74.612	1.0406316	1.8728076
20	0.082	7.454545	0.07454545	67.09091	0.56364	0.105455	67.19636	33.59818	66.402	1.5263158	1.82218
30	0.09	8.181818	0.081818	73.63636	0.074545	0.18	73.81636	36.90818	63.092	1.5671227	1.799973
40	0.099	9	0.09	81	0.081818	0.261818	81.26182	40.63091	59.369	1.6088565	1.7735604
50	0.105	9.545455	0.09545455	85.90909	0.09	0.351818	86.26091	43.13045	56.87	1.6631525	1.7320573
60	0.112	10.18182	0.10181818	91.63636	0.095455	0.447273	92.08364	46.04182	53.958	1.6631525	1.7320573
120	0.12	10.90906	0.10909091	98.18182	0.101818	0.549091	98.73091	49.36545	50.635	1.6934231	1.7044469
180	0.05	3.333333	0.03333333	30	0	0	30	15	85	1.760913	1.9294189
240	0.059	3.933333	0.03933333	35.4	0.033333	0.033333	35.43333	17.71667	82.283	1.248382	1.9153119
300	0.065	4.333333	0.04333333	39	0.039333	0.072667	39.07267	19.53633	80.464	1.2908431	1.9055998
360	0.072	4.8	0.048	43.2	0.043333	0.116	43.316	21.658	78.342	1.3356183	1.8939947
420	0.08	5.333333	0.05333333	48	0.048	0.164	48.164	24.082	75.918	1.3816926	1.8803448
480	0.085	5.666667	0.05666667	51	0.053333	0.217333	51.21733	25.60867	74.391	1.408387	1.8715223
520	0.005	5	0.05	45	0	0	45	22.5	77.5	1.3521825	1.8893017
580	0.003	3	0.03	27	0.05	0.05	27.05	13.525	86.475	1.1311373	1.9368906
640	0.002	2	0.02	18	0.03	0.08	18.08	9.04	90.96	0.9561684	1.9588505

Table 5.12 Dissolution profiles of formulation of F4

Time	Absorbance	C in mcg	C in V made up	C in D.M	Loss	CLA	CDR	%CDR	C%D Retained	Log% CD Released	Log %CD Retained
5	0.059	5.363636	0.0536364	48.27273	0	0	48.27273	24.13636	75.86364	1.3826718	1.88003366
10	0.068	6.181818	0.0618182	55.63636	0.053636	0.053636	55.69	27.845	72.155	1.4447472	1.85826643
20	0.084	7.636364	0.0763636	68.72727	0.061818	0.115455	68.84273	34.42136	65.57864	1.5368281	1.85826643
30	0.091	8.272727	0.0827273	74.45455	0.076364	0.191818	74.64636	37.32318	62.67682	1.5719787	1.79710694
40	0.1	9.090909	0.0909091	81.81818	0.82727	0.274545	82.09273	41.04636	58.95364	1.6132747	1.7705106
50	0.11	10	0.1	90	0.090909	0.365455	90.36545	45.18273	54.81727	1.6549724	1.7389174
60	0.115	10.45455	0.1045455	94.09061	0.1	0.465455	94.55636	47.278181	52.72182	1.67466608	1.72199038
120	0.121	11	0.11	99	0.104545	0.57	993.57	49.785	50.215	1.6970985	1.70083347
180	0.057	308	0.038	34.2	0	0	34.2	17.1	82.9	1.2329961	1.91855453
240	0.067	4.466667	0.0446667	40.2	0.038	0.038	40.238	20.119	79.818	1.3036064	1.90244349
300	0.075	5	0.05	45	0.044667	0.082667	45.08267	22.54133	77.45867	1.3529796	1.88907002
360	0.08	5.333333	0.05333333	48	0.05	0.132667	48.13267	24.06633	75.93367	1.3814099	1.88043437
420	0.085	5.666667	0.0566667	51	0.0533333	0.186	51.186	25.593	74.407	1.4081212	1.87161379
480	0.089	5.933333	0.0593333	53.4	0.0566667	0.242667	53.64267	26.82133	73.17867	1.4284804	1.86438449
540	0.009	9	0.09	81	0	0	81	40	60	1.60206	1.77815125
600	0.0077	0.07	63	0.09	0.09	0.09	63.09	31.45	68.55	1.4976206	1.83600746

Table 5.13 Dissolution profiles of formulation of F5

Time	Absorbance	C in mcg	C in V made up	C in D.M	Loss	CLA	CDR	%CDR	C%D Retained	Log% CD Released	Log %CD Retained
5	0.019	1.727273	0.017273	15.54545	0	0	15.54545	7.772727	92.227273	0.890573	1.9648594
10	0.027	2.454545	0.024545	22.09091	0.017273	0.017273	22.10818	11.05409	88.945909	1.043523	1.949126
20	0.036	3.272727	0.032727	29.45455	0.024545	0.041818	29.49636	14.74818	85.251818	1.168738	1.9307037
30	0.05	4.545455	0.045455	40.90909	0.032727	0.074545	40.98364	20.49182	79.508182	1.31158	1.9004118
40	0.056	5.090909	0.050909	45.81818	0.045455	0.12	45.93818	22.96909	77.030909	1.361144	1.886665
50	0.08	7.272727	0.072727	65.45455	0.050909	0.170909	65.62545	32.81273	67.187273	1.516042	1.827287
60	0.082	7.454545	0.074545	67.09091	0.072727	0.243636	67.33455	33.66727	66.332727	1.527208	1.827279
120	0.085	7.727273	0.07273	69.54545	0.074545	0.318182	69.86364	34.91391	65.068182	.1543221	1.8213687
180	0.038	2.533333	0.025333	22.8	0	0	22.8	11.4	88.6	1.056905	1.9474337
240	0.036	2.4	0.024	21.6	0.025333	0.025333	21.62533	10.81267	89.187333	1.033933	1.9503032
300	0.032	2.13333	0.021333	19.2	0.024	0.049333	19.24933	9.624667	90.375333	0.983386	1.9560499
360	0.036	2.4	0.024	21.6	0.021333	0.070667	21.67067	10.83533	89.164667	1.034842	1.9501928
420	0.03	2	0.02	18	0.024	0.094667	18.09467	9.047333	90.952667	0.956521	1.9588154
480	0.046	3.06667	0.030667	27.6	0.02	0.114667	27.71467	13.85733	86.142667	1.14168	1.9352183
540	0.005	5	0.05	45	0	0	45	22.5	77.5	1.352183	1.8893017
600	0.006	6	0.06	54	0.05	0.05	54.05	27.02	72.98	1.431685	1.8632039
660	0.008	8	0.08	72	0.06	0.06	72.06	36.5	63.95	1.556905	1.8058405
720	0.006	6	0.06	54	0.08	0.08	54.08	27.75	72.925	1.432568	1.8628764

Table 5.14 Dissolution profiles of formulation of F6

Time	Absorbance	C in mcg	C in V made up	C in D.M	Loss	CLA	CDR	%CDR	C%D Retained	Log% CD Released	Log %CD Retained
5	0.048	4.363636	0.43636	39.27273	0	0	39.27273	19.63636	80.364	1.2930611	1.90506
10	0.058	5.272727	0.052727	47.45455	0.043636	0.043636	47.49818	23.74909	76.251	1.375647	1.882245
20	0.062	5.636364	0.056364	50.27272	0.052727	0.096364	50.82364	25.41182	74.588	1.4050357	1.87267
30	0.067	6.090909	0.060909	54.81818	0.056364	0.152727	54.97091	27.48545	72.515	1.4391029	1.860425
40	0.069	6.272727	0.062727	56.45455	0.060909	0.213636	56.66818	28.33409	71.666	1.4523093	1.855313
50	0.072	6.545455	0.065455	58.90909	0.062727	0.276364	59.18545	29.59273	70.407	1.471185	1.847618
60	0.077	7	0.07	63	0.05455	0.341818	63.34182	31.67091	68.329	1.5006605	1.834606
120	0.081	7.363636	0.073636	66.27273	0.07	0.41818	66.68455	33.34227	66.658	1.5229952	1.823851
180	0.048	0.851613	0.032	28.8	0	0	28.8	14.4	85.6	1.1583625	1.932474
240	0.042	0.745161	0.028	25.2	0.032	0.032	35.232	12.61	.87.39	1.1007151	1.941462
300	0.039	0.691935	0.026	23.4	0.028	0.06	23.46	11.7	88.3	1.0681859	1.945961
360	0.0367	0.656452	0.024	22.2	0.026	0.086	22.286	11.14	88.86	1.0468852	1.948706
420	0.042	0.745161	0.028	25.2	0.024	0.11	25.31	12.65	87.35	1.1020905	1.941263
480	0.05	0.887097	0.033	30	0.028	0.128	30.128	15	85	1.1760913	1.929419
520	0.007	7	0.07	63	0	0	63	31.54	68.46	1.4988617	1.835437
600	0.005	5	0.05	45	0.07	0.07	45.07	22.6	77.4	1.3541084	1.888741
660	0.003	3	0.03	27	0.05	0.12	27.12	13.65	86.35	1.1351327	1.936262
720	0.002	2	0.02	18	0.03	0.15	18.15	9.16	90.84	0.9618955	1.958277

- **Post compression evaluation**

In-vitro drug release studies were carried out in dissolution test apparatus type-1 basket, in 900ml of 0.1 N HC1 for first 2hrs, 900ml of phosphate buffer pH7.4 up to 6.8 up to 4hrs and drug release was found to be up to 93.3% in 12hrs. Based on the results of *in-vitro* release studies F4 was selected as optimized formulation in this formulation HPMC E15 is used 40mg and Eudragit L100 in 60 mg more than this amount the drug shows release at the faster rate . due to the various physiochemical properties of HPMCE15. , HPMC E 15 LV was added in all five formulations (F_1-F_6) to improve the perfection and quality of the coating. The purpose of incorporation HPMC E 15 LV to the coating was to improve the physicochemical property of the coating film, such as ductility, toughness and elasticity. (ofori-Kwakye K, Fell JT 2001) (Yuen KH *et al* 1993)Such film may provide expected controlled release of the drug in the small intestine by offering the increased permeability properties of the fluids present in the colon. (Frohoff-Hulsmann *et al* 1999). (Chan LW *et al*2005)Coating with polymer solution more than this concentration was found to be problematic, and significant tablet agglomeration was experienced during coating because of the thermoplasticness and tackiness of the Eudragit coating system.

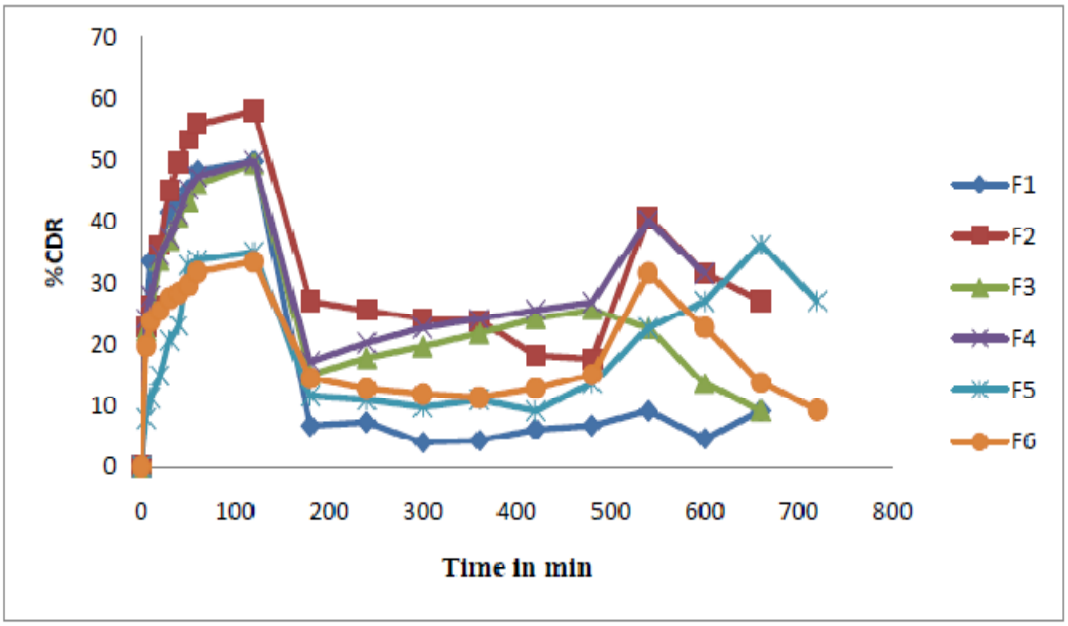


Fig 5.13 Drug release profiles of formulations of F_1 to F_6

5.5.2 Kinetic release models of optimized formulation

To analyse the mechanism of the drug release rate kinetics of the mexilrtine hydrochloride given in the table 5.15, the data obtained were graphed as

1) Cumulative percentage drug released v/s time(*In-vitro* drug release profile)
2) Cumulative percentage drug released v/s Square root of time (Higuchi's plots)
3) Log cumulative percentage drug remaining v/s time (First order release)
4) Log percentage drug released v/s log time (Peppas plots)(Nish demn 2003)

Table 5.14 Kinetics of drug release of R^2 value for F_4 formulation.

Model Name	K Value	R^2 value
Zero order	1.901	0.969
First Order	-0.010	0.977
Peppas model	0.457	0.990
Higuchi model	9.697	0.997

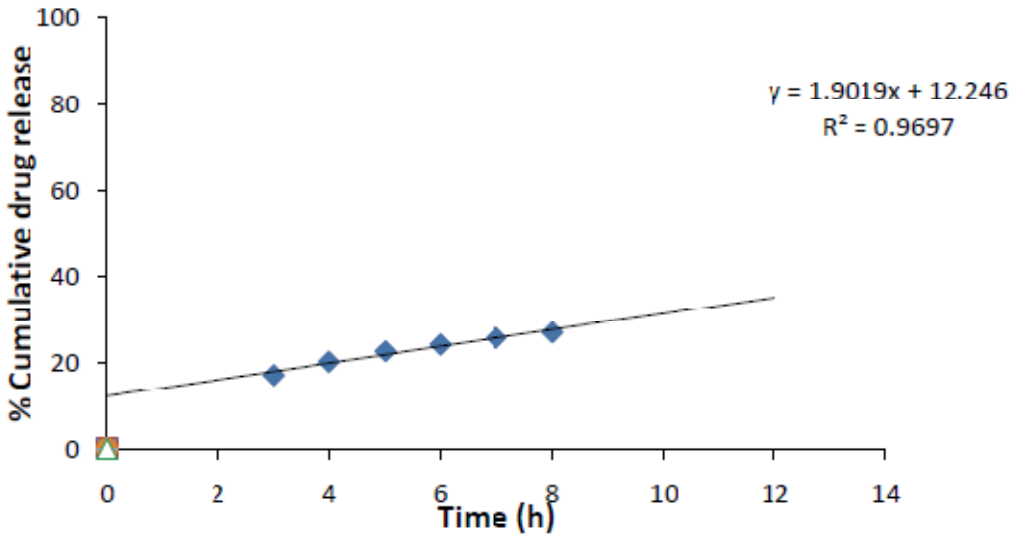


Fig 5.14 Zero order drug release profiles of optimized formulation

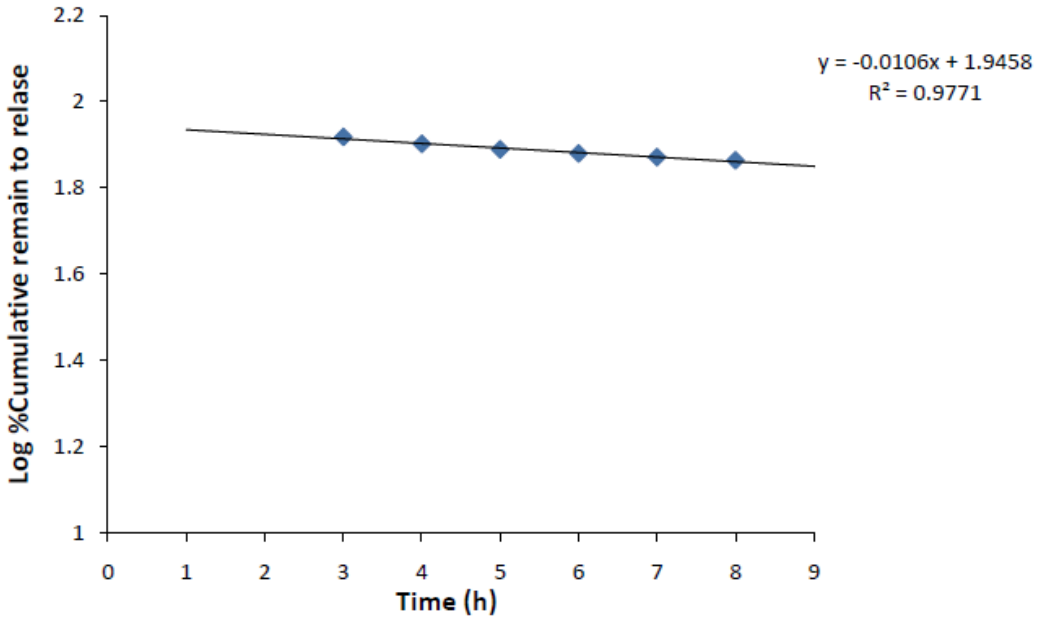


Fig 5.15 First order comparative dissolution profiles of optimized formulation

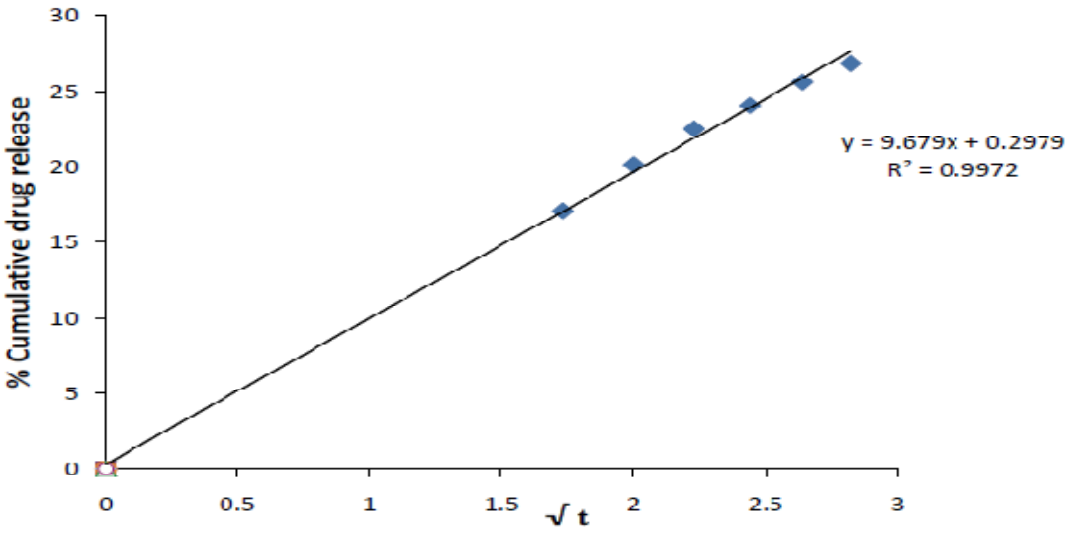


Fig 5.16 Higuchi comparative dissolution profiles of optimized formulation

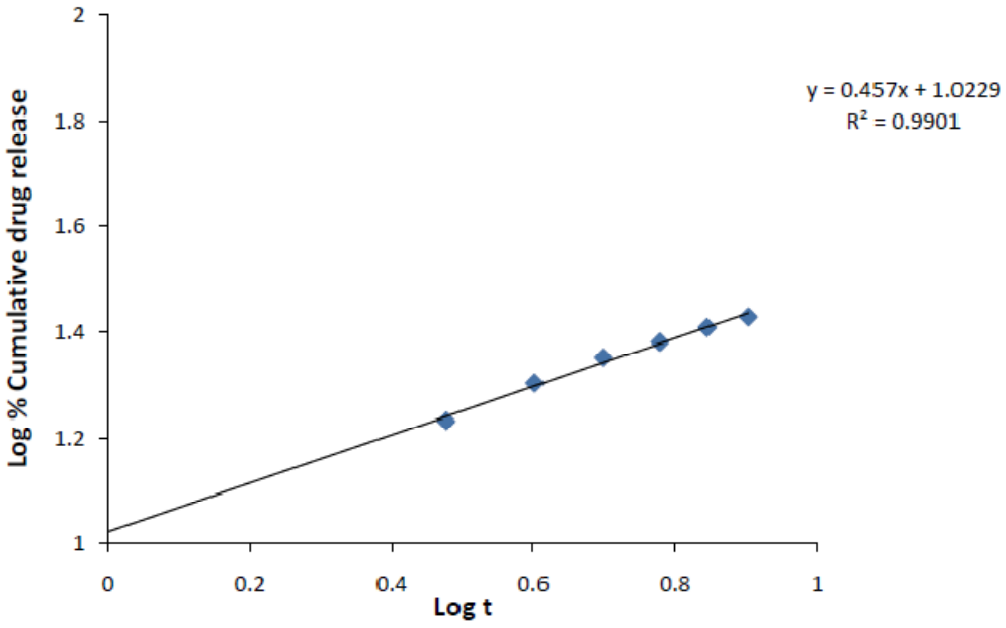


Fig 5.17 Peppas comparative dissolution profiles of optimized formulation

RELEASE MODEL KINETICS DISCUSSION

However, the curve fitting investigations of the release profile gave us useful insight into the mechanism of drug release from the capsule. The release of the drug from the capsule was controlled. The R^2 value of the data obtained from the capsule is the first Order. The release predicts that the drug follows Higuchi model the value of R^2 is 0.997. Investigated formulations were having timed-release profile; therefore keeping in view all the evolutions, F4 was selected. It was expected such a suitable formulation would be useful to achieve the timed-release profile.

5.6 Stability studies

Stability studies were carried out using Thermo lab stability chamber. After 4weeks the optimized formulation was tested for physical appearance, drug content and DSC.

Table 5.14 Stability study analysis

Parameters	**2nd week**	**4thweek**
Physical Appearance	No Change	No Change
Drug content	90.3%	93.3%

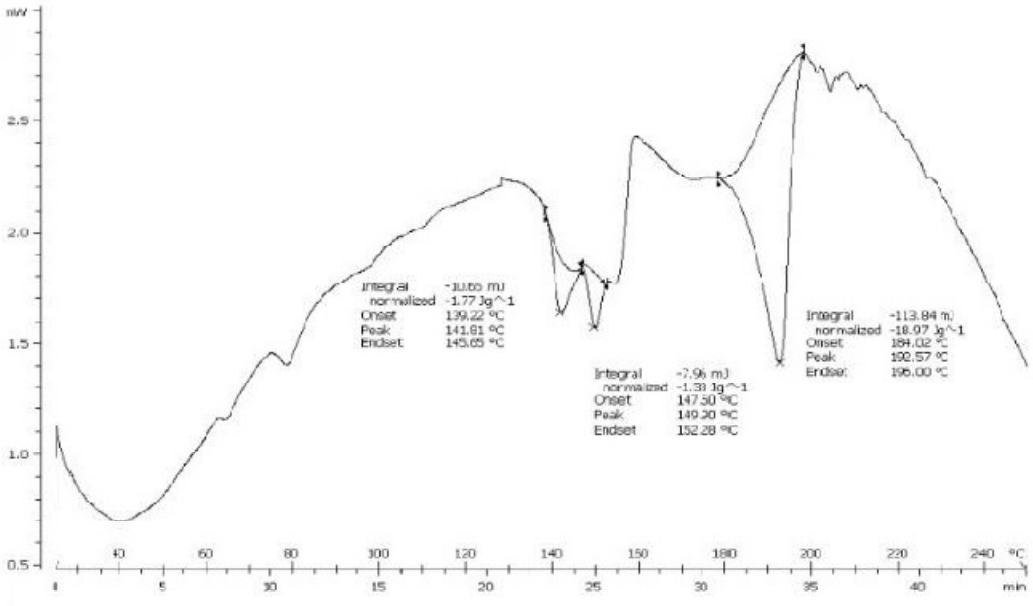


Fig 5.18 DSC graph of formulation IV after stability studies

Discussion:

Granules were kept for accelerated stability study at 40±2◦C and 75±5% RH for 4 weeks in stability chamber. After a period of 4 weeks, the samples were observed for any physical parameters, drug content and DSC. It was observed that there is no change in appearance, drug content and DSC.

6. SUMMARY

A Timed- release delivery system for Mexiletine Hydrochloride was designed to increase its patient compliance by using a suitable polymer. Compared to oral conventional delivery system, the frequency of dosing may be less.

The various pre formulation studies like melting point determination, solubility, and calibration curve of the drug by UV spectroscopy and physico - chemical characteristics of drug have been studied.

The results of all these parameters are tabulated and depicted graphically in the result and discussion section.

Six formulations were prepared by using same drug and polymer in different ratios. The granules were prepared by using the wet granulation technique and were subjected to evaluation of granular properties like angle of repose, bulk density, compressibility index and Hausner's ratio.

Evaluation parameters viz. bulk density, angle of repose, drug content Carr's compressibility index was found to be less than 20% for all the formulations indicating that the powder is compressible. Bulk density and true densities were found to be <1 for all formulation powders.were within acceptable limits for all six formulation.

Results of *in-vitro* release using USP dissolution apparatus indicated that the drug release of formulation F_4 is satisfactory and others it was found to be 50% - 93.3% for 12 hrs respectively.

The results of kinetic drug release of formulation F_4 in the R^2 value was highest for Higuchi model.

Stability study for the granules at 40±2◦C and 75±5% RH for 4 weeks in stability chamber. It was observed that there is no change in appearance, drug content and DSC.

CONCLUSION

The conclusions drawn from the present investigation were given below

- Suitable analytical method based on UV-Visible spectrophotometer was developed for Mexiletine Hydrochloride. 262 nm was identified as an λmax in purified water.
- Timed-release capsules of Mexiletine HC1 were successfully prepared using Lactose, HPMC E15 and Eudragit L 100 by wet granulation method.
- The timed-release capsules were evaluated for pharmacopoeial and non-Pharmacopoeial (industry specified) tests. Based on the results batch F4 was identified as better formulations amongst all formulations for delivering the drug in a pulsatile manner.
- Mexiletine HC1 release from the developed formulations has been observed to be directly proportional to the amount of polymer present in capsules. Capsules of batch F4 passed all official and unofficial quality control tests.
- Data obtained from kinetic treatment revealed F_4 formulation follow Higuchi model.
- Accelerated stability developed formulations were found to be stable.

7. BIBLIOGRAPHY

1. A.J.Cammn.M.D., Electrophysiology, pacing and arrhythmia, clin.cardial.13,349-359(1990).

2. Andrea G, Foppoli A, Sangalli M E. Oral pulsatile delivery systems based on swellable hydrophilic polymers, Eur J Pharm & Biopharm 2008;68:p.11-18.

3. Andrei D, Ahmad M, Development of pulsatile multiparticulate drug delivery system coated with aqueous dispersion Aquacost ® ECD, Int J Pharm 2006; 318:p.124-131.

4. Asano K. -Sameshima T. -Shirasawa H. –Hisamitsu T. Attenuating effect of mexiletinehydrochloride on herpetic pain in mice infected with herpes simplex virus Journal of Pharmacy and Pharmacology 1 Oct 2003.

5. Banker GS, Anderson NR, Tablets. IN: Lachman L,Liberman Ha, Kanig J, editors. The theory and practice of industrial pharmacy 3ered. Mumbai (India): Varghese publishing house;p.293-345.

6. Brahmanker DM and Jaiswal Sb. Biopharmaceutics and Pharmacokinetics-A treatise. 1st edition. VallabhPrakashan, Delhi;2000.p.337.

7. Bruno R, Santoni Y, Iliadis A, Djiane P, Serradimigni A, Cano JP, Simultaneous modelling of mexiletine and hydroxyl-methyl-mexiletine data after single-and multiple-dose administration of a sustained-release mexiletine formulation Biopharm Drug Dispos.1992 Oct;13(7)p.481-493.

8. Chan LW, Ong KT, Heng PW, Novel film modifiers to alter the physical properties of composite ethylcellulose films. Pharm Res 2005;22:476- 89.

9. Chein YW. Normal Drug delivery systems.(NY); Marcel Dekker, INC; 2nd Ed.1992.p.140.

10. Chein YW.Novel Drug Delivery systems.(NY):Marcel Dekker, INC:2nd ed.1922.P.140

11. Drugbank [Internet] June 2005 [Update on April 2011, cited 20 May 2011]; Available from http://www.drugbank/ca/results.

12. Drugbank [Internet] June 2005 [Update on April 2011, cited 20 May 2011]; Available from http://www.drugbank/ca/results (DB00379)

13. Forman D, Webb P,Parsonnet J.H.Pylori and gastric cancer. Lancet 1994;34p.243-54.

14. Forman D.WebbP, Parsonnet J.H.Pylori and gastric cancer. Lancet 1994;34,P.243-54

15. Fukui E, Miyamura N, Uemura N, Kobayashi M. Preparation of enteric coated timed-release press-coated tablets and evaluation of their by invitro and in vivo tests for colon targeting. Int J Pharm 2000;204:p.7-15.

16. Frohoff-Hulsmann MA, Schmitz A, Lippold BC. Aqueous ethyl cellulose dispersion containing plasticizers of different water solubility and hydroxylpropyl methyl-cellulose as coating material for diffusion pellets. I. Drug release rates from coated pellets. IntJ Pharm 1999;177:69-82.

17. GingKuo Wang, Corinna Russell and Sho-Ya Wang.Mexiletine block of wild-type and inactivation-deficient human skeletal muscle hNav 1.4 Na^+ channels February1, 2004 The Journal of Physiology, 554,621-633.

18. Gothoskar AV, Joshi AM,Joshi NH. Pulsatile drug delivery systems: a review. Drug delivery technology 2004; 4(5),p.1-11.

19. Hogan JE Hydroxy propylmethylcellulose. Sustained release technology. Drug devInd Pharm 1989;15,p.975-999.

20. Holt DW, Chadwick DE, Campbell Rw, Absorption and antiarrhythmic efficacy of sustained-release mexiletine. Clin Ther. 1983:5(3):267-78.

21. Hubertus Folttmann and Anisulquadir. Polyvinyl pyrrolidonne-one of the most widely used excipients in pharmaceutics: An overview: Drug delivery technology Jun 2008; vol.8(6).p.244.

22. Hyun Seok Hwang, Can Hasdemir, Derek Laver, DivyaMehra, Kutsal, Turhan MichelaFaggioni, Huiyong Yin, and Bjorn C Knollmann. Inhibition of Cardiac Ca^{2+} Release Channels (RyR2) Determines Efficacy of Class I Antiarrhythmil Drug in Catecholaminergic Polymorphic Ventricular Tachycardia. ArrhythmiaandElectrophysiology (2011) p.128-135.

23. Ishibashi T. Hatono H, Kobayashi M, Mizobe M, Yashino H. Design and evaluation of a new capsule-type dosage form for colon-targeted delivery of drugs. Int J Pharm 1998;168:p.31-40.

24. Ishikawa T, et al. Effect of hydroxyl propylmethylcellulose (HPMC) on the relase profiles and bioavailability of a poorly water-soluble drug from tablets prepared using macrogel and HPMC. Int J Pharm Sci.20;(2000):p.173-8.

25. Leon Lachman, The Theory and Practice of industrial Pharmacy, Sustained Release Dosage Forms,p.430-431. Third edition,1987.

26. Maroni A, Zema L, Cerea M, et al. Expt. Opinion Drug del. 2005; 2, p.855-71.

27. MARY J, Mycek Richard A, Havrvey Pamela C. Lippincott'siiinstrated reviews: Pharmacology; 2nd edition. Lippincott Williams & Wilkins,p.163-165.

28. Medical dictionary Merriam Webster [Internet] 2011 [cited 20 May 2011] Available from http://www.merrian.webster.com/medical/timed-release

29. Medical dictionary Merriam Webster [internet] 2011 {cited 20 May 2011: Available from http://www.merriam.webster.com/medical/timed-release.

30. Nish Dhiman, S.S Poddar, A.Shajahan "Development of matrix and coated units for pH-Independent Release". Nov-2003.

31. Ofori-Kwakye K, Fell JT. Biphasic drug release: The permeability of film containing pectin, chitosan and HPMC. Int J Pharm 2001;226:139-45. [PUBMED]

32. Pozzi, Furlani, Gazzaniga, et al. Journal of Controlled release. 1994;31,p.99-108.

33. Raghuram Reddy K , et al. Once-daily Sustained-release Matrix Tablets of Nicoranddil: formulation and In vitro Evaluation. AAPS Pharm Sci Tech. 2003: 4(4):p.1-9.

34. Raymond C Rowe, Paul J Sheskey and Marian E Quinn. Hand book of pharmaceutical excipients. A joint publication of American pharmaceutical press: Washington; 6thed.2009;p. 206-207,364-367 ,404-406,525-533,728-730.

35. Saita T, Fujito H, Mori M Development of enzyme-linked immunosorbent assay for therapeutic drug monitoring of Mexilitine Biological and pharmaceutical Bulletin, 2003,26(6).p.761-765.

36. Sawada T, Kondo H, Nakashima H, Sako K, Hayashi M Time-release compression-coated core tablet containing nifedipine for chronopharmacotherapy Int J Pharm.2004 Aug 6; 280(1-2).p.103-111.

37. Sawada T, Sako K, Fukui M. Yokohama S, Hayashi M. The core erosion ratio , of compression-coated timed-release tablets predicts the bioavailability of acetaminophen. Int J Pharm 2003;265:p.55-63.

38. Shargel L.Applied Biopharmaceutics & Pharmakokinetics. 5th ed. New York:The McGraw-Hill Companies, Inc;2005.

39. Sharma S, Pawar A. Low density multiparticulate system for pulsatile relase of meloxicam. Int J Pharm 2006;313:p.150-158.

40. Shivakumar HG, Promod Kumar TM, Kashppa GD. Pulsatile Drug delivery system, Indian J PhamEduc 2003;37(3),p.125.

41. Siege, RA and Pitt CG.Journal of controlled release. 1995;33,p.173-188.

42. Survase S, Kumar N.Pulsatile drug delivery:Current Scenario.CRIPS 2007; 8(2):p.29-33.

43. Survase S,Kumar N.Pulsatile drug delivery:Current Scenario.CRIPS 2007; 8(2):p.29-33.

44. Tesuya s, Hiroshi F, Masato M. Development of Enzyme-Linked Immuno Sorbent Assay for Therapeutic Drug Monitoring Of Mexiletine. Bio Pharm Bull 2003;p.266-761.

45. Toyohiro S, Hiromu K, Nakashima H,Sako K, Hayash M. Timed-release compression coated core tablet containing nifedipine for chronopharmacotheraphy. Int J Pharm 2004;280:p.103-111.

46. Tripathi KD. Essential of medical pharmacology. 6th edition. Jaypee brothers medical publishares (p) Ltd, New delhi 2004;p.514.

47. Tripathi KD. Essential of medical pharmacology. 6th edition;p.514.

48. Virtualmedicalcenter [Internet] July 2003 [Updated on july 2006, cited 20 may 2011]; Available from: http://virtualmedicinalcenter.com

49. Xiaoxiong Wei, Renke Dai, Suoping Zhai Kenneth E. Thummel, Fred K. Friedman and Robert E. Vestal inhibition of human liver cytochromep.450 1a2 by the class IB antiarrhythmics Mexiletine, Lidocxaine and Tocainide. JPET May 1999 vol. 289no.2.853-858.

50. Young B Journal of Controlled Release 2004;98,p.337-353.

51. Yuanfeng Gao, et al., Inhibition of late sodium careen by mexiletine: A Novel Pharmotherapeutical Approach in Timothy Syndrome Mar 2013.

52. Yuen KH, Deshmukh AA, Newton JM. Development and in-vitro evaluation of a multiparticulate sustained release theophylline formulation. Drug Dev Ind Pharm 1993;19:855-74.

53. Zeynep A.Muge.S, Tosunoglu S. Spectrophotometric determination of mexilitine Hydrochloride in capsules using bromothymol blue. Turk J Chen 2002 Dec;26(6).p.839-842.